Renal function and atherosclerotic renovascular disease

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PhD thesis, Utrecht University – with a summary in Dutch

ISBN 978-90-3934861l

Cover Katrien van de Camp, Photograph by Jerry Kane "Red starfish in the Pacific Ocean"
Lay-out Haaring Automatisering, Scherpenzeel
Print Gildeprint Drukkerijen B.V., Enschede, the Netherlands

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Nierfunctie en atherosclerotische renovasculaire ziekte

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht
op gezag van de rector magnificus, prof. dr. J.C. Stoof,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen op
vrijdag 29 augustus 2008 des middags te 2.30 uur

door

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geboren op 27 augustus 1974 te Bron, Frankrijk

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The financial support by the Dutch Kidney Foundation for the publication of this thesis is gratefully acknowledged.

Financial support for the publication of this thesis was also provided by the Julius Center for Health Sciences and Primary Care, ImagO (Graduate School for Biomedical Image Sciences), the Röntgen stichting Utrecht, Pfizer bv, Bayer Shering Pharma, Schering-Plough bv, Genzyme Nederland and Boehringer Ingelheim bv.

à ma JoLie famille

Contents

Chapter 1

General introduction

Introduction

The precise prevalence of renovascular disease (RVD) is unknown. Reports vary widely based on the definition used and the population studied. Since it is a potentially reversible cause of renal failure and renovascular hypertension, increasing attention has been devoted to RVD. However, in the absence of definitive clinical trials, there is a lack of evidence regarding the optimal management of this condition.

Further complicating these issues is the fact that RVD is actually a complex disorder with various causes and presentations. The most common causes of RVD are fibromuscular dysplasia (FMD) and atherosclerosis (90%). FMD tends to present in younger females, while atherosclerotic disease is usually seen in older patients with traditional risk factors for atherosclerosis. As our population ages and more patients are surviving the complications of cerebrovascular and coronary atherosclerotic disease, it is likely that the prevalence of atherosclerotic RVD will increase.

The presentation of FMD tends to be straightforward; although these patients may be hypertensive, they generally do not develop renal insufficiency. In contrast, atherosclerotic disease can be exceedingly difficult to evaluate and to manage. These older patients often have co-existent essential hypertension, progressive loss of renal function, and response to renal artery intervention is often sub-optimal. There is a strong association with extrarenal atherosclerotic disease, and as such, patients with atherosclerotic RVD are prone to complications such as stroke, myocardial infarction and cardiovascular death. [1-5]

Renal function, the Cinderella of cardiovascular risk profile

The diagnosis of renal dysfunction is usually based on either an elevated serum creatinine (SCr) or decreased glomerular filtration rate (GFR) or the detection of an elevated urinary excretion of albumin (albuminuria). Whereas elevated SCr points to a reduced GFR, an increased rate of albumin or protein excretion points to a derangement in the glomerular filtration barrier. [6] The finding of a SCr value within normal range can be accompanied by a diminished GFR value, particularly in elderly patients. [7] Microalbuminuria has been shown to correlate with the presence of nephrosclerosis, while the presence of proteinuria generally indicates the existence of established renal parenchymatous damage. [6,8] Besides renal function, the health of the kidneys is reflected by its size. Factors affecting renal size and function include age, gender, body weight, but also hypertension and diabetes mellitus. [9-11]

The traditional risk factors for cardiovascular disease are hypertension, diabetes mellitus, hyperlipidemia and smoking. However, an increased risk of subsequent cardiovascular events is also found among patients with chronic kidney disease (defined as a GFR of less than 60 mL/min per 1.73 m^2) compared to patients with normal renal function. [12] This relationship has mainly been established in elderly patients or in population based studies, but also in subgroups of patients with hypertension, myocardial infarction and congestive heart failure. [13-16]

Furthermore, patients with pre-existing cardiovascular disease have a higher risk of developing new symptoms, and have higher mortality rates than healthy subjects. [17,18] It is gradually becoming evident that renal function has a prominent role in cardiovascular disease.

In ***chapter 2*** we assessed whether atherosclerosis determines the age-related changes in renal size and function and paid attention to the influences of atherosclerosis on renal size and function in patients with manifest atherosclerotic disease. Whether impaired renal function is an independent predictor of cardiovascular disease and death in high risk patients with clinically manifest arterial disease, was established in ***chapter 3***.

Imaging and intervention of the renal artery

The diagnosis of renovascular disease is a challenging venture. The tools at hand are either invasive or non-invasive, and can be divided in imaging tests that rely upon the renal artery anatomy and functional tests, that rely upon the physiologic effects of a renal artery lesion. As far as the patients are concerned, the ideal option would be a non-invasive functional test. A few challenges lay in the fact that the kidneys move with breathing, the renal arteries are affected by atherosclerosis which presents calcifications, and the kidneys come in pairs. Information about blood flow parameters could help detecting hemodynamically significant stenoses and predict which patient would likely benefit from revascularization therapy. [19,20]

Magnetic resonance imaging (MRI) has emerged as a means for assessing renal artery stenosis. [21,22] And beyond morphologic information, MRI-techniques permit characterization of flow dynamics in a non-invasive way. [23] In ***chapter 4*** we established the reproducibility of renal blood flow measurements with phase contrast MRI.

Revascularization of atherosclerotic renal artery stenosis (ARAS) lesions is currently performed with endoluminal stent deployment. [24] Placement of a stent overcomes the obstacle of elastic recoil of the atherosclerotic plaque in the renal artery and early restenosis. Immediate success rates are high and range from 96-100%. [25-28] However, it is estimated that restenosis in the stent is diagnosed in 11-39% of the patients within one year after stent placement. In-stent stenosis is often caused by myointimal hyperplasia and is generally treated with percutaneous transluminal angioplasty and/or placement of a second stent. [25,28]

The direct technical success rate of repeat interventions in the renal artery is high. In ***chapter 5*** we assessed the long-term technical success rates.

Prevention of renal function loss in patients with ARAS

In terms of presentation of the ARAS patient, careful differentiation between the following three terms is essential. First, ARAS which refers to the anatomical presence of an obstructive renal artery lesion due to atherosclerosis. Second, renovascular hypertension (RVH) referring to usually renin-dependent hypertension that occurs as the direct physiological result of ARAS. [29] And third, ischemic nephropathy (IN) which refers to the progressive loss of renal function due at least in part to the global renal ischemia. [30]

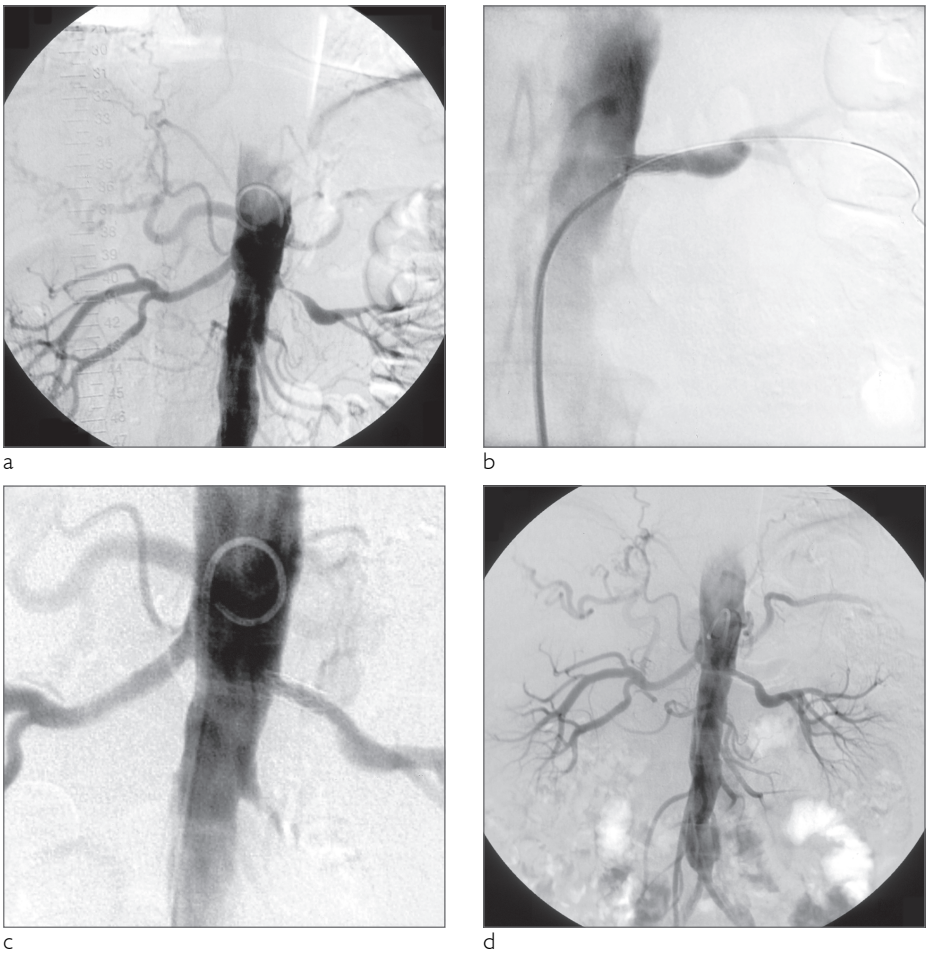
The demonstration of an ARAS in a patient with hypertension or renal dysfunction does not necessarily constitute RVH or IN. Clinically non-significant (asymptomatic) ARAS is often found incidentally in patients with essential hypertension, renal failure of various etiologies, or even in those with normal blood pressure.

Recently, ideas are accumulating that atherosclerotic damage in the kidney, independently of a stenosis, could cause the renal function to be impaired. [31-35] This is called *atherosclerotic nephropathy*. The fact that patients with a stenosis due to FMD usually have normal renal function reinforces this hypothesis. The differences between the atherosclerotic and the FMD patient are the older age and the presence of atherosclerosis. Progressive renal failure may furthermore occur despite successful revascularization, suggesting that its cause may be lying within the kidney instead of the proximal stenosis. Increasing age and essential hypertension can be other causes of damage in the renal parenchyma, these are called *nephrosclerosis*. [36, 37] Unfortunately, histology is not able to differentiate between ischemic nephropathy, atherosclerotic nephropathy and nephrosclerosis as the histological changes are non-specific. [33]

The question remains whether in ARAS patients, conservative management is indicated rather than revascularization therapy. The controversy derives primarily from the difficulty in balancing the clinical benefits against the considerable risks of vascular intervention for individual patients.

Drugs with documented value for preventing cardiovascular events, including antihypertensive, lipid-lowering and antiplatelet agents, contribute to the primary objectives of ARAS treatment. The impact of medical therapy for ARAS patients has evolved over time. With the advent of angiotensin-converting enzyme inhibitors and calcium channel blockers, more than 80% of patients in several series have demonstrated excellent blood pressure control. [38] From the three recent prospective randomised trials comparing the treatment of ARAS with percutaneous transluminal angioplasty (PTA) versus medication, it appears that PTA offers little advantage over medical therapy unless the hypertension is refractory or there is progressive azotemia. [39-41] Technical improvements in endovascular approaches have dramatically improved our ability to intervene in ARAS over the last several years (figure). A recent meta-analysis demonstrated that renal arterial stent placement resulted in almost equal percentages of renal function improvement, deterioration and stabilisation. [42] However, stent placement procedures are not free of complications. [43-46] In about 5% of the patients serious complications occur that require intervention and 1% of the stent placements is complicated by loss of renal function and the need for renal replacement therapy. Mortality of stent placement in RVH patients averages 1%. Whether stent placement can achieve a similar reduction in the progression of renal failure as optimal medical lipid and blood pressure therapy is unknown.

Chapter 6 describes the protocol of the STAR study, a randomised trial comparing medical treatment to medical treatment plus stent placement in ARAS patients with impaired renal function. The primary outcome was defined as a more than 20% reduction in creatinine clearance. The two-years outcomes are evaluated in ***chapter 7***.



a b c d

Figure. Severe renal artery stenosis of the left renal artery with post-stenotic dilation **(a).** The stenosis is subsequently revascularised by PTA with stent placement. Figure **b** shows the result after stent placement. The patient was followed-up angiographically showing a patent left artery and stent 6 and 18 months after initial stent placement (figures **c** and **d** respectively).

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Part I

Renal function, the Cinderella of cardiovascular risk profile

Chapter 2

Influence of atherosclerosis on age-related changes in renal size and function

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on behalf of the SMART Study Group

Eur J Clin Invest 2003; 33:34-40

Abstract

Background

Renal size and function reflect the health of the kidney. These parameters are associated with age, gender and body weight. The kidneys are also influenced by micro- and macrovascular diseases. Atherosclerotic markers and risk factors may influence the age-related changes of renal size and function.

Methods

Data of 1056 patients who entered the SMART-study (Second Manifestations of ARTerial disease) were used to assess the effect of atherosclerosis on the relationship between age and renal size and function and to study the effect of atherosclerosis on renal size and function. Patients who were newly referred to the hospital with manifestations of vascular disease were screened for asymptomatic atherosclerosis with noninvasive tests. The carotid intima-media thickness (IMT) and albuminuria were used as estimates for the atherosclerotic burden. Renal size was defined as the mean pole-to-pole length of both kidneys measured by ultrasonography. Renal function was represented by serum creatinine.

Results

Intima-media thickness was a significant effect modifier of the age-renal size relationship ($P = 0.041$). The increase of serum creatinine with age was more pronounced in the highest tertile of IMT ($P = 0.048$). Renal size decreased equally with age in patients with and without hypertension or diabetes mellitus (DM). The same held true for the age-renal function relationship. Albuminuria and DM were independent predictors of renal size and function.

Conclusion

Atherosclerosis accelerates the decrease of renal size and the increase of serum creatinine with age. Renal size and function are determined by albuminuria and DM.

Introduction

Renal size and function are easily measured parameters that both reflect the health of the kidney. Factors related to renal size and function include age, gender and body weight. [1-3] The kidneys are, however, also influenced by micro- and macrovascular diseases. Decreased renal function is associated with hypertension, diabetes mellitus (DM), smoking and hyperlipidaemia but also with cardiovascular disease and presence of atherosclerotic renal artery stenosis. [4-8] Most of these studies have, however, been conducted in healthy or older subjects or in a selection of patients with diabetes or dyslipidaemia. Less is known about the factors that influence renal size. The size of the kidney is also thought to be influenced by DM and hypertension. [3,4,9] Renal artery stenosis may cause shrinkage of the kidney as a result of ischaemic renal disease, although causality has not yet been established. [10,11] Atherosclerosis could also affect the small renal vessels resulting in a decrease in renal size and function. [12]

The aim of this study was to assess whether the severity of atherosclerosis determines the age-related changes of renal size and function and influences renal size and function in patients with manifest atherosclerotic disease.

Materials and methods

Study design and patients

All patients were participants of the Second Manifestations of ARTerial disease (SMART) study; an ongoing, single-center prospective cohort study of patients referred to the University Medical Center Utrecht for the first time because of manifest atherosclerotic vascular disease (peripheral arterial disease, transient ischaemic attack or minor stroke, internal carotid artery stenosis, angina pectoris, myocardial infarction, diabetic foot as a result of ischaemia, abdominal aortic aneurysm or renal artery stenosis) or for treatment of atherosclerotic risk factors (hypertension, DM, hyperlipidaemia). The main objectives of the SMART study are to determine the prevalence of additional vascular disease and risk factors in patients presenting with a manifestation of vascular disease or a risk factor, and to study predictors for future cardiovascular events. Patients aged 80 years and older and those with a terminal malignancy were not enrolled. Details on the study design have been described elsewhere. [13] The results reported here were obtained from the entry visit of the patients and hence are based on a cross-sectional study design. The study was approved by the medical Ethics Committee and written informed consent was obtained from all study participants. For the purpose of this study we selected SMART patients aged 40 years and older with manifest atherosclerotic vascular disease because of their more pronounced atherosclerosis (n = 1185).

Risk factors

The patients were asked to fill in a questionnaire about their prior medical history (hypertension and DM among others) and symptoms of cardiovascular disease and risk factors. Height and weight were measured. The blood pressure was recorded using a semiautomatic oscillometric device (Omega 1400, Invivo Research Laboratories Inc., Broken Arrow, OK, USA). Laboratory samples were taken to determine the lipid profile (cholesterol, triglycerides, HDL and LDL cholesterol), renal function (creatinine) and glucose from venous blood and creatinine and microalbumin from urine. Albuminuria was considered as a marker for atherosclerotic vessel damage and was calculated as the ratio of albumin to creatinine (mg albumin per mmol creatinine).

Non-invasive assessment of atherosclerosis and renal length

The patients were screened for asymptomatic atherosclerosis by noninvasive tests. The intima-media thickness (IMT) of the left and right common carotid artery was examined in anterolateral, posterolateral, and mediolateral directions with an ATL Ultramark 9 (Advanced Technology Laboratories, Bethel, WA, USA) equipped with a 10-MHz linear array transducer. Intima-media thickness was defined as the average of these six measurements performed on both sides, in millimetres. The IMT was taken as the surrogate measure for the burden of generalized atherosclerosis. Ultrasonography of the abdomen was performed with an ATL 3000 HDI (Advanced Technology Laboratories) equipped with a 4-MHz curved array transducer to measure a.o. the length and volume of the left and right kidney. The length of the kidney was the maximum length on a longitudinal image. Ultrasound measurements were routinely performed by multiple investigators of our research-oriented vascular diagnostic laboratory. The intra- and interobserver coefficients of variation were 7.7% and 11.7% for the IMT measurements, respectively. [14] The intra- and interobserver standard deviation of the difference of the measurements with corresponding 95% limits of agreement were 0.69 cm (-1.36; 0.99) and 0.61 cm (-1.27; 1.13) for the renal length measurements, respectively. [15] Renal size was the average length of the two kidneys in millimetres and was, together with renal function, used as the outcome of the analysis.

Hypertension was defined as treatment for hypertension or newly measured hypertension. The definition of hypertension was a systolic blood pressure ≥160 mmHg or a diastolic blood pressure ≥95 mmHg. [16] Diabetes mellitus (DM) was defined as treatment for DM or newly detected DM (fasting glucose ≥7.0 mmol/L, nonfasting glucose ≥11.1 mmol/L). [17]

Data analysis

Mean renal lengths of 80 mm and less (shrivelled kidneys, n = 4) and those exceeding 140 mm (n = 6) were excluded from the analysis, as were patients who were primarily included because of renal artery stenosis. A total of 1056 patients had complete data. Multivariate linear regression analysis was used to assess the effect of atherosclerosis (albuminuria and IMT, both continuous), hypertension and DM (both dichotomous) on renal size and function and on the relationship between age and kidney length on the one hand and age and kidney function on the other hand. Because the serum creatinine was not normally distributed, the natural log (ln) was used in the analysis. The regression coefficient ß is interpreted as an increase of the outcome variable, with ß when the determinant increases with one unit. For the outcome ln of serum creatinine, ß × 100 is by approximation of the percentage change in serum creatinine (µmol/L) with the increase of the determinant with one unit. The duration of the presence of hypertension and DM was expressed in years. To assess the modifying effect of IMT, hypertension and DM, the statistical significance of the product term of age and IMT, hypertension or DM was determined. Analyses were adjusted for known confounders: gender and body mass index (weight divided by the square length) for renal length and gender and weight for renal function. Probability values of less than 0.05 were considered significant.

Results

Baseline characteristics of the study population are given in Table 1. The majority of the patients was male (76%) and the mean age of the participants was 61 years. Fifty-two percent of the participants had hypertension and 20% were known to have DM. More than three-quarters of the patients were past or current smokers.

After correcting for body mass index and gender, renal length decreased with 0.251 mm when age increased with one year (95% CI 0.200; 0.302; Table 2). Adjustment for IMT, hypertension or DM did not change the coefficient of age (Table 2). Taking into account the duration of the presence of hypertension and DM did not influence the magnitude of the relationship either. The IMT modified the relationship between age and renal size (P = 0.041), but hypertension and DM did not (P = 0.5 and 0.2, respectively). The modifying effect of IMT is illustrated by Table 3 and Figure 1. In the lowest tertile of IMT, the mean renal length decreased with 0.163 mm per year of age compared with 0.299 mm and 0.329 mm per year of age in the median and upper tertiles, respectively.

Table 1. Baseline characteristics of the study population

Characteristics	n = 1056
Age (years)	61 (53–69)
Male sex	76.0
Inclusion diagnosis	
Peripheral arterial disease	29.2
Coronary artery disease	29.4
Cerebrovascular disease	31.2
Abdominal aortic aneurysm	10.2
Cardiovascular risk factors	
Smoking past or current	83.6
Body mass index (kg/m^2)	26 (24–28)
Systolic blood pressure (mmHg)	141 (127–157)
Diastolic blood pressure (mmHg)	78 (72–85)
Hypertension*	51.6
Diabetes mellitus†	20.4
Hyperlipidaemia‡	81.3
Mean common carotid intima- media thickness (mm)	0.90 (0.77–1.08)
Microalbuminuria (mg/mmol)	0.7 (0.4–1.5)
Renal parameters	
Mean right kidney length (mm)	111 (105–118)
Mean left kidney length (mm)	111 (105–118)
Serum creatinine (µmol/L)	90 (79–102)

Values are percentages or medians with interquartile range in parenthesis.
* Systolic pressure ≥160 mmHg, diastolic pressure ≥95 mmHg, prior history of or treatment for hypertension.
† Fasting serum glucose ≥7.0 mmol/L, nonfasting glucose ≥11.1 mmol/L, prior history of diabetes mellitus or treated with insulin or oral blood sugar lowering drugs.
‡ Total cholesterol ≥6.5 mmol/L, triglycerides ≥2.3 mmol/L, HDL cholesterol ≤1.0 mmol/L, prior history of hyperlipidaemia or on lipid-lowering drugs.

Table 2. Regression analyses of age and mean renal length, and of age and renal function. The models are adjusted for atherosclerotic markers (albuminuria and IMT) and atherosclerotic risk factors (hypertension and diabetes mellitus)

	Mean renal length (mm)		Renal function (ln creatinine)	
	Regression coefficient ß*	95% CI	Regression coefficient ß†	95% CI
Age (years)	-0.251	-0.302; -0.200	0.0063	0.005; 0.007
Age adjusted for IMT (mm)	-0.253	-0.309; -0.197	0.0059	0.005; 0.007
Age adjusted for albuminuria (mg/mmol)	-0.249	-0.300; -0.198	0.0059	0.005; 0.007
Age adjusted for hypertension	-0.246	-0.298; -0.194	0.0059	0.005; 0.007
Age adjusted for diabetes mellitus	-0.260	-0.311; -0.210	0.0065	0.005; 0.008

Renal function is expressed as the natural logarithm (ln) of serum creatinine (µmol/L).
* Regression coefficient is adjusted for gender and body mass index. It describes the change in renal length (mm) per unit change in the explanatory variable (age).
† Regression coefficient is adjusted for gender and weight. ß × 100 by approximation describes the percentage change in serum creatinine (µmol/L) per unit change in the explanatory variable (age).
IMT, intima-media thickness.

Table 3. Relation between age and renal size, and between age and renal function in different subgroups of atherosclerosis

	Mean renal length (mm)		Renal function (ln creatinine)	
	Regression coefficient ß*	95% CI	Regression coefficient ß†	95% CI
Age				
1st Tertile of IMT	-0.163	-0.260;-0.065	0.0043	0.001; 0.008
2nd Tertile of IMT	-0.299	-0.391;-0.207	0.0061	0.003; 0.008
3rd Tertile of IMT	-0.329	-0.442;-0.217	0.0085	0.006; 0.012

* Regression coefficient is adjusted for gender and body mass index. It describes the change in renal length (mm) per unit change in the explanatory variable (age).
† Regression coefficient is adjusted for gender and weight. ß × 100 by approximation describes the percentage change in serum creatinine (µmol/L) per unit change in the explanatory variable (age).
P-value of the product term of age and IMT is 0.041 for renal length and 0.048 for renal function.
1st tertile = IMT <0.80 mm, 2nd tertile = IMT 0.80–1.02 mm, 3rd tertile = IMT ≥1.02 mm.
IMT, intima-media thickness.

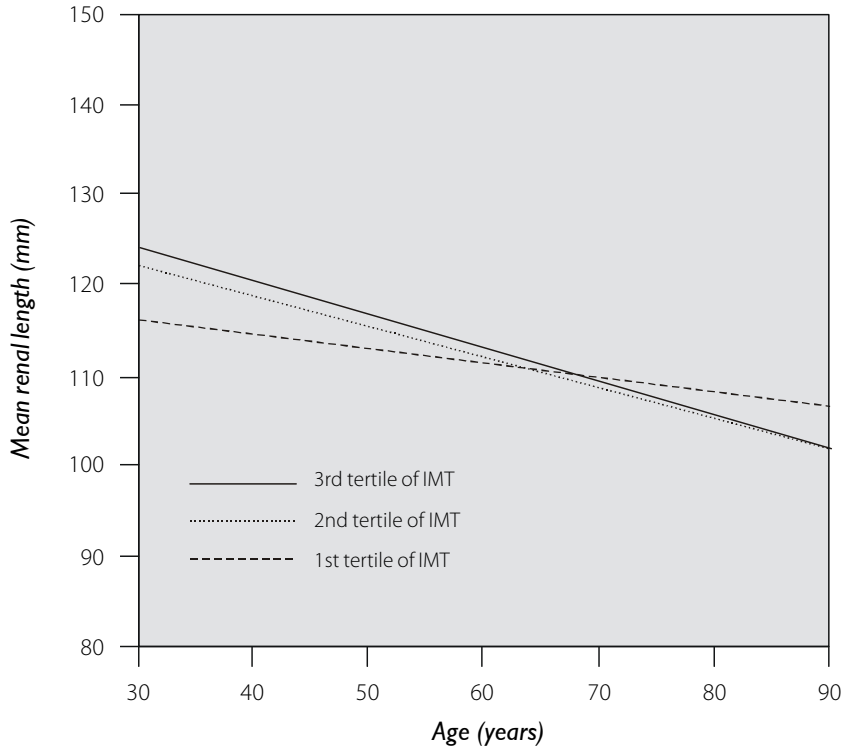

Figure 1. Illustration of the modifying effect of intima-media thickness (IMT) in the regression analysis of age (years) and mean renal length (mm). The decrease of renal length with age is more pronounced in patients in the higher tertile of IMT than in those in the lower tertile of IMT.

After correcting for gender and weight, the serum creatinine increased by approximately 0.6% with the increase of age with one year (95% CI 0.005; 0.007; Table 2). Adjustment for IMT, hypertension or DM did not change the age-renal function relationship (Table 2). Taking into account the duration of the presence of hypertension and DM did not influence the relationship either. Intima-media thickness modified the age-renal function relationship (P = 0.048), but hypertension and DM did not (P = 0.13 and 0.13, respectively). The modifying effect of IMT is illustrated by Table 3 and Figure 2. Serum creatinine increased approximately by 0.4% per year of age in the lowest tertile of IMT compared with 0.6% and 0.8% per year of age in the median and upper tertiles, respectively.

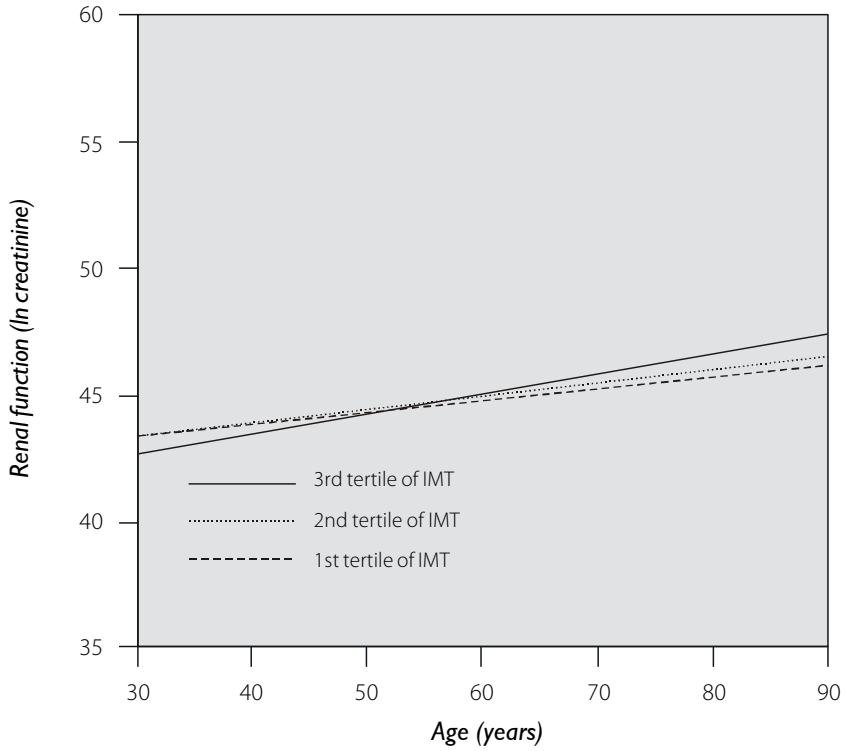

Figure 2. Illustration of the modifying effect of intima-media thickness (IMT) in the regression analysis of age and renal function. The increase of renal function (ln creatinine) is more pronounced in patients in the higher tertile of IMT than in those in the lower tertile of IMT.

Table 4a shows the factors that were independently associated with kidney size. Patients with DM have on average 3.6-mm larger kidneys than patients without DM, independently of the level of albuminuria. The independent determinants of renal function are shown in Table 4b. Patients with hypertension have on average an approximately 3.3% higher serum creatinine than normotensives, while diabetics have an approximately 5.3% lower serum creatinine level than nondiabetics.

Table 4. Determinants of mean renal length (**a**) and renal function (**b**)

a	Mean renal length (mm) ‡	
	Regression coefficient ß *	95% CI
Age	-0.085	-0.263; 0.092
Male sex	5.7	4.5; 6.8
BMI	0.51	0.37; 0.65
IMT	13.3	0.5; 26.0
IMT × age	-0.20	-0.39; -0.01
Albuminuria	-0.036	-0.063; -0.010
DM	3.6	2.4; 4.9
b	**Renal function (ln creatinine) §**	
	Regression coefficient ß *	95% CI
Age	0.0010	-0.003; 0.005
Male sex	0.19	0.16; 0.22
Weight	0.0016	0.001; 0.003
IMT	-0.34	-0.63; -0.06
IMT × age	0.0053	0.001; 0.010
Albuminuria	0.0032	0.002; 0.004
Hypertension	0.034	0.011; 0.057
DM	-0.053	-0.081; -0.024

* Regression coefficient describes the change in renal length (mm) per unit change in the explanatory variable.
† Regression coefficient × 100 approximately describes the percentage change in serum creatinine (µmol/L) per unit change in the explanatory variable.
IMT, intima media thickness; DM, diabetes mellitus; ln, natural logarithm.
‡ Intercept 97.6 (95% CI 85.8; 109.3), and § Intercept 4.2 (95% CI 3.9; 4.4).

Discussion

This study showed that neither the atherosclerotic markers expressed as IMT and albuminuria nor the atherosclerotic risk factors as hypertension and DM had an additional effect on the age-related changes in renal size and function. In the patients with a higher atherosclerotic burden (thicker IMT) the mean renal size, however, decreased more with age compared with the patients with a lesser atherosclerotic burden (thinner IMT). Comparably, the increase in serum creatinine was more pronounced in the patients with more severe atherosclerosis.

To assess the effect of atherosclerotic factors on the age-related changes of renal size and function, we selected patients with clinically manifest vascular disease. These patients had more severe atherosclerosis and thus formed a population in which an effect of atherosclerosis was more likely to be found. Furthermore, in this population an effect of hypertension or diabetes would be more easily assessed because the patients with and without these diseases were comparable and unselected. Patients with manifest atherosclerosis are rarely younger than 40 years. We excluded these patients from the analysis because no judgement could be given on the relationship between age and renal size/function in this subgroup. Moreover the decrease in renal size with age would not yet be present in patients aged under 40 years. [18]

Intima-media thickness was used as a surrogate measure of the burden of generalized atherosclerosis. Intima-media thickness has been associated with cardiovascular risk factors such as age, smoking, hypertension and hypercholesterolaemia. [19] Changes in IMT are related to atherosclerotic lesions in other arterial beds. [20] These findings support the view that carotid IMT measurements can be used as an indicator of generalized atherosclerosis, reflecting the probability of the presence of atherosclerotic lesions in other arteries. [21,22] Similarly, albuminuria is a marker of early atherosclerosis. [23] An increased urine albumin excretion is associated with an unfavourable cardiovascular risk profile, but its pathogenesis is currently unknown. [24] Most studies use microalbuminuria (albuminuria ≥0.2 mg/mmol) as a parameter. But with such a threshold, subtle influences of increasing levels of albuminuria cannot be detected. [24] We therefore preferred to use albuminuria.

A higher atherosclerotic burden accelerates the decrease of both renal size and function with age. Renal size and function were furthermore both independently determined by albuminuria. Renal shrinkage has so far mainly been studied in association with renal artery stenosis (RAS). [25] Most natural history studies consider the decline in renal length as a consequence of the, often progressive, stenosis. [10,25] But the studies that have made a distinction between RAS as a result of atherosclerosis and fibromuscular dysplasia (FMD) actually demonstrated that the luminal reduction apparently is not the factor responsible for the decrease in kidney size. They found that patients with FMD had relatively larger kidneys and that even with a progressive stenosis they did not show a significant decrease in kidney size. [11,26]

The differences between the patients with atherosclerotic RAS and the patients with fibrodysplastic RAS are the older age and the presence of extensive atherosclerosis especially at the kidney level. [27,28] These are in fact the two factors that we studied here. The incidence of asymptomatic and unsuspected RAS in the atherosclerotic population is high and ranges from 22 to 40%. The results of this study cannot rule out a role of atherosclerotic RAS in the decrease in kidney size, as its incidence in this study population is unknown. It appears that in a certain number of patients atherosclerotic RAS is responsible for a decrease in the renal length of the ipsilateral kidney. [10] Whether atherosclerotic RAS causes renal dysfunction is increasingly being questioned. The limited ability of revascularization procedures to restore renal function and studies demonstrating that renal insufficiency is independent of (the severity of) a stenosis suggest that atherosclerotic damage in the kidney itself has a role in renal function impairment.

Atherosclerosis is considered to be a generalized disease. Atherosclerotic lesions of the microvasculature of the kidney (called atherosclerotic nephropathy) cause glomerulosclerosis, interstitial fibrosis and tubular atrophy, and finally a reduction in the number of glomeruli, resulting in a decrease in renal mass and function. Increasing age and essential hypertension are other causes of damage in the renal parenchyma, and are called nephrosclerosis. The damage caused by atherosclerosis is, however, very similar to that caused by age and hypertension. [29] Our data suggest that the effect of age is in fact accelerated in more severe atherosclerosis.

Patients with hypertension or DM are at increased risk for atherosclerotic vascular disease. Diabetes mellitus is often complicated by diabetic nephropathy, which is characterised by microvascular lesions and is marked by microalbuminuria and renal dysfunction. Hypertension can cause direct damage to the kidney. [12] In this study, we have demonstrated that renal function is independently determined by hypertension, DM and albuminuria, which is in accordance with other reports. [1,5,6] Patients with DM seemed to have on average lower levels of creatinine. An explanation might be that in patients with DM, renal function impairment is essentially mediated by albuminuria. Progression of renal insufficiency has been attributed to diabetic nephropathy rather than to DM. [30] Diabetic kidneys have been reported to be enlarged in the early and later stages of the disease, which is supported by our data. [9,31]

In conclusion, our data demonstrate that atherosclerosis defined as carotid IMT accelerates the decrease of renal size with age and the increase of serum creatinine with age. Renal size and function decrease equally with age in patients with and without hypertension or DM. Atherosclerosis assessed as albuminuria is a predictor of renal size and function. Results of this study suggest that generalized atherosclerosis has an independent effect on the health of the kidneys.

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Chapter 3

Renal function as a risk indicator for cardiovascular events in 3216 patients with manifest arterial disease

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In press Atherosclerosis (DOI: 10.1016/j.atherosclerosis.2007.12.006)

Abstract

Aim

To establish whether impaired renal function is an independent predictor of cardiovascular disease (CVD) and death in an unselected high-risk population with CVD.

Methods and results

In 3216 patients with CVD, the estimated glomerular filtration rate (GFR) was assessed with the Modification of Diet in Renal Disease-equation. Primary outcomes were all vascular events (including stroke, myocardial infarction, end-stage renal disease and vascular death) and all cause death. During a median follow-up of 39 months, 378 patients had a vascular event (11.7%) and 337 patients died (10.5%). The adjusted hazard ratio (HR) of an estimated GFR ≤60 vs. >90 mL/min per 1.73 m^2 was 1.8 (95% CI, 1.2-2.6) for vascular events and 1.4 (95% CI 0.9-2.0) for all cause death. For stroke and cardiac events as separate outcomes, similar HR's were found. Subgroup analysis according to localization of vascular disease at presentation or presence of the risk factors hypertension, diabetes and albuminuria had no influence on the hazard ratios.

Conclusions

The presence of moderate to severe renal insufficiency is an independent risk factor for adverse CVD events in high-risk patients with a history of vascular disease. Localization of vascular disease or presence of other risk factors had no influence on the impact of renal function alone.

Introduction

Chronic renal disease is increasingly being recognised as a serious public health problem as approximately one out of 20 patients will eventually progress to end-stage renal failure necessitating renal replacement therapy such as dialysis or renal transplantation. [1]

The association between renal insufficiency and cardiovascular disease (CVD) was first shown in patients with end-stage renal disease, whose cardiovascular mortality exceeds that of patients without renal disease by a factor 10-30. [2,3] Even in young adults with end-stage renal disease the cardiovascular mortality is high. [4] Therefore, the impact of renal insufficiency on the development of atherosclerotic CVD probably may already begin with minor renal dysfunction.

Renal insufficiency has been proposed as an independent predictor of CVD and all-cause mortality. This has been studied in several subgroups, essentially in the elderly or general population, but also in selected patients with hypertension, survivors of myocardial infarction or patients with congestive heart failure. [5-11] Few studies have examined the relationship of impaired renal function and recurrence of CVD in patients with pre-existing CVD. [12,13] The aim of this report was to establish whether impaired renal function is an independent predictor of CVD and death in unselected high-risk patients with clinically manifest arterial disease.

Patients and methods

Study design and patients

All patients were participants of the Second Manifestations of ARTerial disease (SMART) study, an ongoing, single center prospective cohort study in patients with manifest atherosclerotic vascular disease (peripheral arterial disease, transient ischemic attack (TIA) or minor ischemic stroke, angina pectoris, myocardial infarction, abdominal aortic aneurysm (AAA) or ischemic renal disease) or cardiovascular risk factors (hypertension, diabetes mellitus, hyperlipidemia). Starting in 1996, consecutive patients aged 18 to 80 years, referred to the University Medical Center Utrecht (UMCU) with manifest arterial disease or a cardiovascular risk factor underwent a vascular screening including a questionnaire, blood chemistry and ultrasonography. Main objectives of the SMART study are to determine the prevalence of additional vascular disease and risk factors and to study predictors for future cardiovascular events. Details on the study design have been described elsewhere. [14] The study was approved by the medical ethical committee and written informed consent was obtained from all study participants.

For the purpose of this report we selected patients with manifest arterial disease who entered the study between September 1996 and March 2005, and excluded the patients enrolled because of ischemic renal disease (89 patients). This study involved a total of 3216 patients.

Risk factors

The patients were asked to fill in a questionnaire about their medical history (hypertension and diabetes mellitus among others) and symptoms of CVD and risk factors. Height, weight and blood pressure were recorded. Fasting laboratory samples were taken to determine the lipid profile (cholesterol, triglycerides, HDL and LDL cholesterol), creatinine, homocysteine and glucose concentration from blood and creatinine and albumin from urine, respectively.

Hypertension was defined as (newly) measured hypertension (systolic blood pressure ≥160 mmHg or a diastolic blood pressure ≥95 mmHg) or treatment for hypertension. Diabetes mellitus (DM) was defined as (newly) established fasting glucose concentration ≥7.0 mmol/L, non-fasting glucose ≥11.1 mmol/L or when the patient used oral medication for diabetes or insulin. Albuminuria was calculated as the ratio of albumin to creatinine in urine (mg albumin per mmol creatinine). Microalbuminuria was defined as an albumin-to-creatinine ratio >2.5 mg/mmol.

Renal function

To estimate the glomerular filtration rate, we used the abbreviated Modification of Diet in Renal Disease (MDRD) equation incorporating age, race, sex and serum creatinine level: [15] GFR (mL/min per 1.73 m^2) = 186 × (SCr [μmol/L] ÷ 88) $^{-1.154}$ × (Age [years]) $^{-0.203}$.

For women and blacks, the product of this equation was multiplied by a correction factor of 0.742 and 1.21, respectively. Serum creatinine was measured in venous blood with a commercial enzymatic dry chemistry kit (Johnson and Johnson). The distribution of the estimated GFR was divided into three categories: less than 60 (moderately to severely decreased GFR), 60 to 89 (mildly decreased GFR) and at least 90 mL/min per 1.73 m^2 (normal GFR), incorporating the guidelines of the National Kidney Foundation. [1]

Follow-up

Questionnaires were sent to the patients, with questions on hospitalisation and out patient clinic visits, on a half-yearly basis. Outcomes of primary interest in this study were death of all causes and vascular events, including stroke, coronary ischemic events, rupture of abdominal aneurysm, end-stage renal disease, amputation of lower extremities, vascular death and the composite of these vascular events, considering whichever occurred first. Definitions have been described previously. [14] When a possible event was recorded, hospital discharge letters and results of relevant laboratory and radiology examinations were collected. With this information, all events were audited by three members of the SMART study Outcome Event Committee, comprising physicians from different disciplines.

Data-analysis

The follow-up time was truncated on March 1st 2005, resulting in a median follow-up of 39 months. To study the effects of renal function on vascular events and mortality we fitted Cox proportional hazards models to the data. We analysed the association between renal function and each outcome event in three categories of GFR, >90, 60-90 and ≤60 mL/min per 1.73 m^2. The group of subjects with an estimated GFR above 90 mL/min per 1.73 m^2 was used as a reference. Analyses were adjusted for age, gender, body mass index (weight in kilograms divided by the square height in meters) and presence of hypertension. Additional adjustment was performed for coronary artery disease, cerebral disease, peripheral artery disease, AAA, diabetes mellitus, smoking and the use of angiotensin converting enzyme (ACE) inhibitor and angiotensin-II (A-II) antagonist medication. Results are summarized as hazard ratios (HR) with 95% confidence intervals. The cumulative incidence of vascular events was illustrated by an estimated survival curve (1 minus survival) assessed by the Cox-regression model and adjusted for all the above mentioned variables. We furthermore analysed the relationship of renal function with vascular events and all cause death in subgroups of patients according to localization of pre-existing vascular disease and presence of hypertension, diabetes mellitus or microalbuminuria. To assess the modifying effect of the subgroups, the statistical significance of the product term of the estimated GFR and that factor was determined. Probability values of less than 0.05 were considered statistically significant.

Results

The baseline characteristics of the study population according to renal function are presented in Table 1. Moderate to severely impaired renal function was present in 517 (16%) patients, while mild renal impairment was present in the vast majority of the patients (n=2097, 65%). Subjects with an estimated GFR below 60 mL/min per 1.73 m^2 were older and were more likely to have hypertension and microalbuminuria.

During follow-up a total of 378 patients had at least one vascular event (11.7%) and 337 patients died (10.5%). The majority of the vascular events consisted of nonfatal strokes, myocardial infarction and sudden death. Death was of vascular origin in 65% of the cases.

Subjects with an estimated GFR below 60 mL/min per 1.73 m^2 were at significantly greater risk for a vascular event compared with subjects with normal renal function. For these subjects, the HR adjusted for age, gender and body mass index, was 1.8 (95% confidence interval [CI], 1.3-2.6, Table 2). After additional adjustment for hypertension and other cardiovascular risk factors the HR was 1.8 (95% CI 1.2-2.6). Figure 1 illustrates the cumulative incidence of vascular events over time according to the degree of glomerular filtration rate. The adjusted HR for all cause death was 1.4 (95% CI 0.9-2.0) in subjects with an estimated GFR below 60 mL/min per 1.73 m^2. In subjects with a mild decreased renal function, no significant increased risk for vascular event or all cause death was found.

Table 1. Baseline characteristics of the 3216 patients with symptomatic CVD

	MDRD* (mL/min per 1.73 m²)			*P*-value†
	> 90 n= 602	> 60 - ≤ 90 n= 2097	≤ 60 n= 517	
Age (yrs)	54 (10)	60 (10)	67 (8)	<0.001
Male gender (%)	83	77	64	<0.001
BMI (kg/m²)	26.7 (4.3)	26.7 (3.7)	26.5 (3.9)	0.4
Coronary artery disease‡ (%)	51	56	51	0.015
Cerebrovascular disease‡ (%)	28	29	35	0.008
Peripheral artery disease‡ (%)	29	24	30	0.006
Aneurysm of the abdominal aorta‡ (%)	8	10	23	<0.001
Hypertension‡ (%)	42	48	71	<0.001
Diabetes Mellitus‡ (%)	26	20	25	<0.001
Smoking present/past (%)	86	82	78	0.002
Estimated GFR (mL/min/1.73 m²)	104 (18)	76 (14)	48 (13)	-
Serum creatinine (μmol/L)	72 (9)	90 (12)	141 (87)	-
Microalbuminuria (%)	15	14	36	<0.001
Medication (%)				
ACE inhibitor	14	19	33	<0.001
A-II antagonist	5	4	8	<0.001

Values are percentages or means with standard deviation in parenthesis.
* Modification of Diet in Renal Disease (MDRD) in mL/min per 1.73 m². >90: normal renal function; >60 & ≤90: mild decrease in renal function; ≤60 moderate to severe decrease in renal function.
† Chi-square test for discrete variables and t-tests for continuous variables.
‡ Based on inclusion criteria or medical history.

We also considered stroke (either ischemic or hemorrhagic) and cardiac events as separate outcomes. Patients with severe renal dysfunction had an increased risk of developing these events compared with the reference group. After adjustment for the other cardiovascular risk factors the HR's were 1.9 (95% CI 1.0-3.7) for stroke and 1.8 (95% CI 1.0-3.0) for cardiac events (Table 2).

In subgroups of patients according to the localization of prior vascular disease or presence of a vascular risk factor, the risk of a vascular event increased with decreasing estimated GFR. In patients with diabetes the relative risk for a vascular event was 2.8 (95% CI 1.3-6.0) in subjects with an estimated GFR below 60 mL/min per 1.73 m² versus 1.4 (95% CI

Table 2. Adjusted HR for vascular events, stroke, ischemic stroke, cardiac event and death

		No. of subjects	No. of events	HR I* (95% CI)	HR II* (95% CI)	HR III* (95% CI)
Vascular event †						
MDRD	> 90	602	47	1.0	1.0	1.0
	> 60 - ≤ 90	2097	217	1.0 (0.7 - 1.4)	1.0 (0.8 - 1.5)	1.1 (0.8 - 1.5)
	≤ 60	517	114	1.8 (1.3 - 2.6)	1.8 (1.3 - 2.7)	1.8 (1.2 - 2.6)
Death						
MDRD	> 90	602	41	1.0	1.0	1.0
	> 60 - ≤ 90	2097	186	0.8 (0.6 - 1.1)	0.8 (0.6 - 1.1)	0.9 (0.6 - 1.2)
	≤ 60	517	110	1.4 (0.9 - 2.0)	1.3 (0.9 - 2.0)	1.4 (0.9 - 2.0)
Stroke						
MDRD	> 90	602	15	1.0	1.0	1.0
	> 60 - ≤ 90	2097	59	0.9 (0.5 - 1.7)	0.9 (0.5 - 1.7)	1.0 (0.5 - 1.7)
	≤ 60	517	38	2.2 (1.2 - 4.3)	2.0 (1.0 - 3.8)	1.9 (1.0 - 3.7)
Cardiac event						
MDRD	> 90	602	25	1.0	1.0	1.0
	> 60 - ≤ 90	2097	136	1.2 (0.8 - 1.9)	1.3 (0.8 - 2.1)	1.4 (0.9 - 2.2)
	≤ 60	517	55	1.7 (1.0 - 2.9)	1.9 (1.1 - 3.2)	1.8 (1.0 - 3.0)

* HR I: Hazard ratio adjusted for age, gender and body mass index; HR II: Hazard ratio adjusted for age, gender, body mass index and hypertension, HR III: Hazard ratio adjusted for age, gender, body mass index, hypertension, coronary artery disease, cerebral disease, peripheral artery disease, AAA, diabetes mellitus, smoking and the use of ACE inhibitor and A-II antagonist medication.

† A vascular event is the composite of stroke, coronary ischemic events, rupture of abdominal aneurysm, end-stage renal disease, amputation of lower extremities or vascular death, whichever occurs first.

0.9-2.2) in those without diabetes (Table 3). However, diabetes mellitus was not a statistically significant effect modifier because the p-value of the interaction term is 0.5 as is also shown by the largely overlapping confidence intervals. The product term of the estimated GFR with albuminuria had a p-value of 0.7 and that with AAA a p-value of 0.1. In the other subgroups of patients, HR's were similar with overlapping confidence intervals in all categories, indicating the absence of an effect of localization of prior vascular disease and cardiovascular risk factor on the hazard ratio estimates. Subgroup analyses considering all cause death demonstrated no influence of the subgroup factors on the HR's (data not shown).

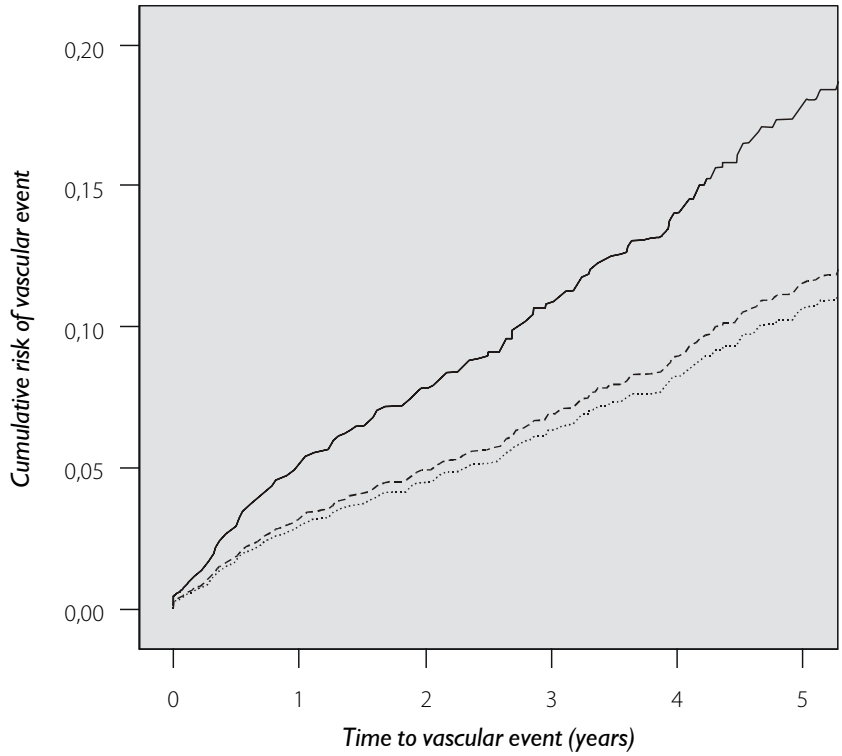

Figure 1. Estimated survival curves for vascular events in MDRD-categories (adjusted for age, gender, body mass index, hypertension, coronary artery disease, cerebrovascular disease, peripheral artery disease, AAA, diabetes mellitus, smoking and the use of angiotensin converting enzyme ACE inhibitor and A-II antagonist medication). Dotted line: estimated GFR <90 mL/min per 1.73 m^2; dashed line: estimated GFR >60 and ≤90 mL/min per 1.73 m^2; continuous line: estimated GFR ≤60 mL/min per 1.73 m^2.

Discussion

In the current study we showed that among a large unselected cohort of patients with CVD an estimated GFR below 60 mL/min per 1.73 m^2 is associated with an increased risk of a recurrent vascular event. In subgroups of patients according to localization of vascular disease or presence of the risk factors hypertension, diabetes mellitus and microalbuminuria, similar risk implications of GFR were found for the occurrence of vascular events and death.

The pathophysiological pathway of the effect of renal function on recurrent CVD remains unclear. There may be several explanations. (i) Atherosclerosis is a progressive, generalised and multifactorial disease where symptoms and manifestations of vascular disease usually parallel the severity of atherosclerosis. Atherosclerosis affects the arteries of larger as

Table 3. Adjusted HR of moderate to severe renal impairment (MDRD ≤60 mL/min per 1.73 m^2) versus normal renal function (MDRD >90 mL/min per 1.73 m^2) for vascular events, in subgroups of patients

	No. of subjects	No. of events	HR I* (95% CI)	HR II* (95% CI)	HR III* (95% CI)
Coronary artery disease					
absent	1480	184	2.1 (1.3 - 3.6)	2.0 (1.2 - 3.3)	1.8 (1.0 - 3.0)
present	1736	194	1.5 (0.9 - 2.6)	1.6 (1.0 - 2.8)	1.7 (1.0 - 3.0)
Cerebrovascular disease					
absent	2261	237	1.7 (1.1 - 2.7)	1.8 (1.1 - 2.8)	1.7 (1.0 - 2.7)
present	955	141	2.0 (1.1 - 3.8)	1.9 (1.0 - 3.6)	1.8 (1.0 - 3.5)
Peripheral artery disease					
absent	2377	261	1.9 (1.2 - 2.9)	1.9 (1.2 - 3.0)	1.8 (1.1 - 2.8)
present	839	117	1.7 (0.9 - 3.2)	1.7 (0.9 - 3.2)	1.6 (0.8 - 3.1)
Aneurysm of abdominal aorta					
absent	2837	289	1.6 (1.1 - 2.5)	1.7 (1.1 - 2.5)	1.6 (1.0 - 2.4)
present	379	89	2.4 (0.9 - 6.2)	2.3 (0.9 - 6.1)	2.6 (1.0 - 7.2)
Hypertension					
absent	1577	157	2.2 (1.2 - 3.9)	2.2 (1.2 - 3.9)	2.1 (1.1 - 3.7)
present	1617	215	1.7 (1.0 - 2.8)	1.7 (1.0 - 2.8)	1.6 (1.0 - 2.7)
Diabetes					
absent	2500	265	1.6 (1.1 - 2.6)	1.6 (1.0 - 2.4)	1.4 (0.9 - 2.2)
present	692	109	3.2 (1.5 - 6.7)	3.2 (1.5 - 6.8)	2.8 (1.3 - 6.0)
Albuminuria					
< 2.50 mg/mmol	2515	248	1.8 (1.1 - 2.9)	1.8 (1.1 - 3.0)	1.8 (1.1 - 2.9)
> 2.50 mg/mmol	536	105	0.9 (0.5 - 1.8)	0.9 (0.5 - 1.8)	0.9 (0.5 - 1.9)

* HR I: Hazard ratio adjusted for age, gender and body mass index; HR II: Hazard ratio adjusted for age, gender, body mass index and hypertension, HR III: Hazard ratio adjusted for age, gender, body mass index, hypertension, coronary artery disease, cerebral disease, peripheral artery disease, AAA, diabetes mellitus, smoking and the use of ACE inhibitor and A-II antagonist medication.

well as smaller calibre at the same time. The presence of kidney disease might be a marker of the atherosclerotic process, especially small vessel disease (target organ damage), caused by traditional risk factors as hypertension or diabetes. (ii) Decreased renal function may accelerate atherosclerosis, resulting in the earlier development of recurrent CVD. [16] (iii) The altered balance of extracellular calcium and phosphorous concentration commonly seen in patients with chronic renal failure are resulting in extensive vascular calcification, thereby contributing to the substantially increased risk of cardiovascular death. [17] (iv) Renal function loss has been associated with endothelial dysfunction, which predicts cardiovascular events. [18] (v) It has been suggested that the effect of renal function on vascular events may in part be mediated through inflammation. [19] (vi) And finally, because of the presence of renal insufficiency, patients might receive less aggressive therapy (underutilization of aspirin, beta-blockers and ACE-inhibitors) because of an assumed higher risk of complications such as bleeding (through platelet dysfunction) and aggravation of renal dysfunction. [20] These patients might thus receive inappropriate treatment for vascular disease and risk factor modification.

Cardiovascular events have strongly been associated with renal function in community-based studies (subjects considered at low risk) as well as in patients with cardiovascular risk factors (high risk) or in selected patients with established CVD (highest risk). In a community-based cohort, subjects with moderate renal insufficiency had a 38% excess risk for incident atherosclerotic complications compared with subjects with normal renal function (HR 1.38, 95% CI 1.02-1.87). [21] A pooled analysis of community-based studies in subjects without a history of CVD showed an excess risk of 19% for subjects with chronic kidney disease compared to those without (HR 1.19, 95% CI 1.07-1.32). [22] In a hypertensive population, a baseline GFR of less than 53 mL/min per 1.73 m^2 was associated with a 32% higher risk for coronary heart disease compared with a GFR > 104 mL/min per 1.73 m^2. [23] In a recent report on a large population of patients with myocardial infarction, a 10 ml lower GFR was associated with a 10% increase in risk of death or incident cardiovascular events. [10]

Few studies have addressed this issue in unselected patients with established CVD. In accordance with our results, they showed that patients with renal insufficiency had a substantially increased risk for cardiovascular death and total mortality. In the Heart Outcomes and Prevention Evaluation (HOPE) study, a randomized clinical trial including patients with objective evidence of vascular disease or diabetes with another cardiovascular risk factor, cardiovascular and all-cause mortality rates were nearly twice as high in patients with increased serum creatinine concentration (≥ 124 µmol/L). [13] This trial, however, included mostly patients from the cardiology and diabetes clinic and therefore still contains a selected group of patients. Moreover, the fact that the patients were selected to participate in a therapeutic trial, makes the results less generalizable. A pooled analysis of four large community-based studies, including subjects with pre-existing CVD, showed that patients with an estimated GFR below 60 mL/min per 1.73 m^2 had a significantly increased risk of myocardial infarction, fatal coronary heart disease, stroke and all cause death (HR 1.35, 95%CI 1.21-1.52). [12]

The HR's for the occurrence of vascular events or all cause death found here are slightly higher than in the previously described studies. [12, 13] This might be explained by the fact that earlier studies used a dichotomized variable for renal insufficiency whereas we used three categories of renal function. The contrast between the groups is then less strong and results in lower HR's. Both studies furthermore adjusted their analyses for all the traditional risk factors. Usually, adjustment is performed for factors that are associated with the exposure as well as the outcome. Adjusting for such factors, however, also implies that they do not lie in the pathway between the exposure and the outcome and thus might explain part of this association. Little is known about these complex relationships, and therefore the factors adjusted for in the multivariate analysis between renal function and CVD should be selected with care.

All analyses were adjusted for traditional risk factors including age, gender, hypertension and diabetes, but also for potential confounders including history of vascular disease, smoking and the use of reno-protective drugs such as ACE inhibitors and A-II antagonists. As demonstrated in Tables 2 and 3, correcting for these factors did not change the hazards of renal function. The increased risk of renal impairment for vascular events is independent of these variables. To further assess the role of hypertension and diabetes, but also the impact of vascular disease according to its localization, we performed subgroup analyses and found no statistically significant difference between the HR's in the different subgroup. Presence or absence of these factors thus did not alter the relationship between renal function and the outcome event. Although not significant, there was a tendency for diabetics to have a higher risk for vascular events if the renal function was moderately to severely impaired. This might in part be explained by the simultaneous occurrence of diabetes and proteinuria which are associated with a higher cardiovascular risk. [24] Microalbuminuria is associated with increased mortality and cardiovascular events. [25] In our patients with microalbuminuria, moderately to severely impaired renal function was not associated with an increased risk for vascular events (HR 0.9 with a 95% CI 0.5-1.9). In fact albuminuria and renal function are very closely related as they are both markers of chronic kidney disease, which is why we did not consider albuminuria as a potential confounder. This subgroup analysis demonstrates that the impact of renal impairment is already comprised in microalbuminuria and that renal function loss (assessed by the MDRD equation) does not add to that risk anymore. Although presence or absence of an AAA did not have a statistically significant influence on the relationship between renal function and occurrence of vascular events, there seemed to be an increased risk with presence of AAA. This might be explained by the fact that patients with AAA often have concomitant renal artery disease and thus decreased renal perfusion. This might lead to decreased renal function. However, the data of our study can not confirm this causal hypothesis.

We found an increased risk for vascular events and all cause death in patients with moderate to severe renal impairment (estimated GFR ≤60 mL/min per 1.73 m^2), but not in patients with mild renal impairment (estimated GFR 60-89 mL/min per 1.73 m^2). However, several studies have demonstrated that mild renal failure carries an increased risk for cardiovascular events and death in community based cohorts and patients with cardiovascular risk factors. [6,26,27] Also the HOPE-trial including patients with established CVD demonstrated an increased risk for cardiovascular events and death for mild renal insufficiency. [13] This was however defined as a serum creatinine > 124 µmol/L or creatinine clearance <65 mL/min. According to the clinical guidelines of the national kidney foundations, these are thresholds for moderately to severely decreased GFR and are in fact the same thresholds that we used in this study. [1] Moreover more severe renal dysfunction is often missed with the use of serum creatinine measurements. [15,28] As stated before, mild renal insufficiency might have an effect on the development of atherosclerotic CVD and it might accelerate atherosclerosis. Our findings suggest that once patients have established CVD, severely impaired renal function increases their risk for future or recurrent cardiovascular events.

The major strength of our study is that it consists of a large cohort of unselected and ambulatory high risk patients. Our population thus includes patients with coronary artery disease, cerebrovascular disease, peripheral artery disease as well as AAA. Patients were recruited and followed-up in a standardised way allowing to study the risk of renal function in several subgroups of disease categories and for different outcome events (i.e. stroke and cardiac events). For a more accurate means of estimating the GFR, we used the modification of diet in renal function (MDRD) equation which has recently been demonstrated to better estimate the true GFR than the Cockcroft-Gault formula. [15]

Our study, however, has several limitations. Firstly, we were not able to assess the effect of renal function in subcategories below an estimated GFR of 60 mL/min per 1.73 m^2 because the number of patients in these categories was too small. The threshold of 60 mL/min per 1.73 m^2 is generally considered the definition of chronic kidney disease, but as demonstrated by other reports, the risk of CVD sharply continues to increase with decreasing estimated GFR. Secondly, our baseline data were acquired on a single day. We thus have no information on the course of renal function or the duration of renal impairment at baseline and could not address the influence of these factors on the outcome.

In summary, the presence of moderately to severely renal insufficiency is an independent risk factor for adverse CVD events in patients with a history of vascular disease. Localization of vascular disease or presence of other risk factors as hypertension, diabetes or albuminuria had no influence on the impact of renal function alone.

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Part II

Imaging and intervention of the renal artery

Chapter 4

Renal blood flow measurements using phase contrast magnetic resonance imaging: normal values and reproducibility

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J Vasc Interv Radiol 2005; 16(6):807-14

Abstract

Purpose

To assess the validity and the direct, short-term, and long-term reproducibility of renal blood flow (RBF) measurements with phase-contrast (PC) magnetic resonance (MR) imaging.

Materials and methods

In 20 healthy volunteers, RBF measurements were repeated with and without repositioning. Internal validity was assessed by comparing the total RBF with the difference in aortic flow above and below the renal arteries. In 19 healthy volunteers RBF measurements were performed at two different occasions. In 40 healthy volunteers, RBF measurements were performed to assess normal values as a function of age. Analyses were performed according to Bland and Altman.

Results

The technical success rate ranged from 78 to 85%. Total RBF and the difference in aortic flow rates showed good agreement (Pearson correlation coefficient, 0.72; $P = 0.002$). Directly repeated measurements had a mean difference of 54 mL/min in total RBF with a coefficient of variation (CV) of 17%. For repeated measurements with repositioning, the mean difference in total RBF was 74 mL/min (CV, 23%). Repeated measurements on different occasions showed a CV of 20%. The mean total RBF of the 40 healthy volunteers was 838 mL/min ± 244 (SD).

Conclusion

RBF measurement with PC MR has a success rate greater than 75%. The demonstrated internal reliability of this method and fair reproducibility of the flow parameters is crucial for further studies of the renal artery with MR imaging.

Introduction

Decreased renal blood flow (RBF) may lead to deterioration of renal function and is thought to cause renal shrinkage. [1-4] Knowledge on flow parameters is crucial in detecting hemodynamically significant stenoses and in predicting which patients with renovascular disease are likely to respond to revascularization therapy. [5,6] During the past decade, contrast material-enhanced three-dimensional magnetic resonance (MR) angiography has emerged as a means for assessing renal artery stenosis. [7,8] Beyond morphologic information, MR techniques permit direct quantitative characterization of flow dynamics in a non-invasive way. [9-11] The phase contrast (PC) technique provides velocity maps that allow determination of the mean velocity of blood across the lumen of a vessel during the cardiac cycle.

To be able to determine the potential and value of two-dimensional PC MR imaging for flow measurement applications, knowledge about its reliability in terms of validity and reproducibility is essential. Validity refers to the extent to which the measurements are meaningful and appropriate. Reproducibility quantifies the measurement error (direct reproducibility), evaluates hemodynamic variations (short-term reproducibility) and determines variations of imaging conditions and scanner drift (long-term reproducibility). Insight into normal values in healthy subjects is important to estimate the biological variations between and within subjects. The aim of this study was to establish the direct, short-term and long-term reproducibility of RBF measurements with PC MR imaging and to determine the normal values of RBF.

Materials and Methods

Study design and volunteers

The structure of the study is depicted in Figure 1. To assess the direct and short-term reproducibility of RBF, repeated flow measurements were performed in 20 healthy volunteers. For the direct reproducibility of the measurement, a second acquisition was performed without changing the position of the subject and with use of the same scan plan. Subsequently, to assess internal validity, total RBF was measured by calculating the difference in aortic flow above and below the level of the renal arteries. To determine the short-term reproducibility a third measurement was performed after the volunteers were moved out of the gantry, and moved back into the gantry. A scan plane was subsequently chosen based on a new planning scan. To study the long-term reproducibility, RBF measurements were performed two times at different occasions in 19 volunteers with a median interval of 11 days (interquartile range 7-21). The investigators were blinded to the name and previous results in the renal arteries. The measurements were all performed by one researcher (L.B.). In addition, to determine the normal RBF, MR flow measurements were assessed in a total of 40 healthy volunteers. Because future RBF measurements are more likely to be indicated in patients of

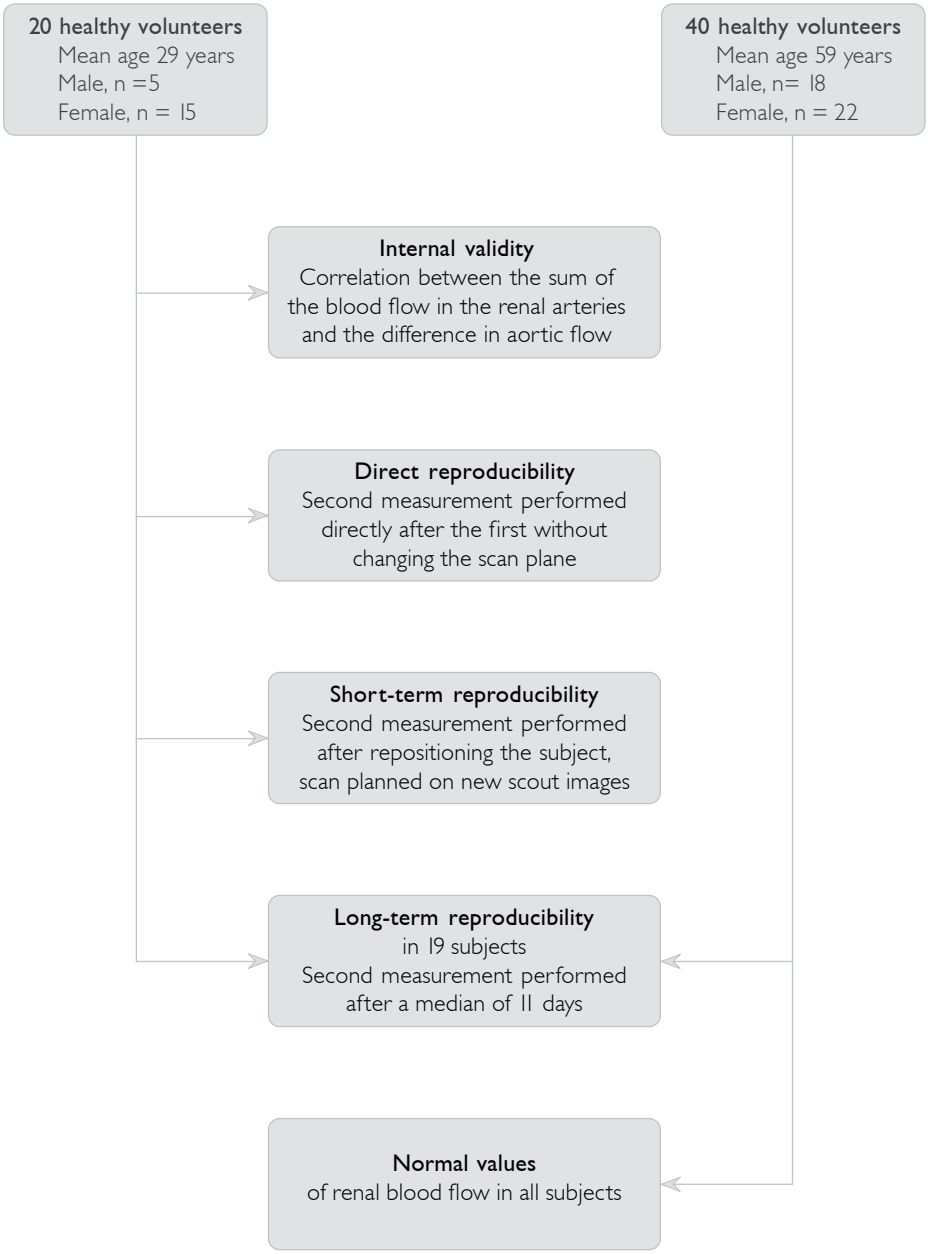

Figure 1. Outline of measurements in healthy volunteers.

older age, we selected subjects aged 40 years or older. In these 40 subjects renal parenchymal volumes were measured and renal function was assessed. The volunteers were all healthy and had no previous history of renal disease, cardiovascular disease or cardiovascular risk factors, and also used no medication. The creatinine concentrations of the volunteers was unknown to the investigators at the time of the measurements of the renal artery. The study was approved by the hospital's medical ethics review committee and informed consent was obtained from all participants.

Acquisition techniques

All imaging was performed on a 1.5-T Philips MR system (Gyroscan NT; Philips Medical Systems, Best, The Netherlands) with a synergy body coil for signal reception.
To localize the renal arteries, a coronal balanced turbo field echo scout image was obtained at the level of the kidneys. A T2-weighted turbo spin-echo imaging was performed in coronal orientation to measure renal volume. Imaging parameters included a repetition time of 2508 msec, echo time of 120 msec, flip angle 90°, turbo factor of 17, six signals averaged, a 178 x 256 matrix, a field-of-view of 30 cm, and 5-mm slice thickness without intersection gap.

Subsequently, non-cardiac-gated three-dimensional PC MR angiography was performed for morphological assessment of the renal arteries. [12] Spoiled gradient-echo images were obtained in the transverse plane with the following parameters: repetition time of 15 msec, echo time of 5 msec; flip angle of 20°; two signals averaged; 62.5% partial echo sampling; field of view of 26 cm; 163 x 256 acquisition matrix, and 45-cm/sec flow-encoded velocity in all directions.

For each renal artery, an oblique section as described by Schoenberg et al. was positioned on the axial course of the vessel to obtain an in-plane view. [13] Cine PC MR flow measurements were then obtained perpendicular to the vessel axis. Cine PC flow measurements were performed with cardiac triggering with use of retrospective synchronization. The scan plane was set perpendicular to the renal artery approximately 10-15 mm distal to the ostium. A segmented turbo field echo scan was performed with the following image parameters: repetition time of 8.9 msec, echo time of 4.7 msec, flip angle of 25°, field of view of 20 cm, slice thickness 6 mm, matrix of 208 x 256, two signals averaged, turbo factor of 4, and a flow-encoded velocity of 100 cm/sec. Twenty time frames were retrospectively reconstructed per heart cycle. Flow in one renal artery was measured in approximately 2 minutes during continuous breathing. Because the spatial resolution of flow measurement allowed reliable display of only vessels with larger diameters, the measurements were limited to the main renal arteries, thereby disregarding accessory renal arteries and lumbar arteries.

For internal validation of the measurements, in the direct reproducibility study, flow data were also obtained in the abdominal aorta superior and inferior to the origins of the renal arteries. The scan parameters for measurement of the aortic flow were as follows: repetition time of 16 msec, echo time of 3.7msec, flip angle of 25°, field of view of 35 cm, slice thickness of 5 mm, matrix of 352 x 512, one signal averaged, and a flow-encoded velocity of 120 cm/sec. Sixteen time frames were reconstructed per heart cycle. To avoid inclusion of the superior mesenteric artery, the position of the slices was carefully planned on the maximum-intensity projections of the non-gated three-dimensional PC MR angiography sequence. With accurate flow measurements, the sum of the flow volumes in the renal arteries should equal the difference of flow volumes measured in the aorta superior and inferior to the origins of the renal arteries.

Post processing techniques

To analyze the flow measurements, an elliptical region of interest was manually drawn generously around the vessel in one heart phase by one observer (L.B.) and copied to the other phases. Visually, all phases were screened to correct positioning of the region of interest; it was adjusted if necessary. The flow volume was calculated by averaging the flow velocity values within the contour and multiplying with the area. Mean flow (in mL/min) in each vessel was calculated as the average of the flow rates for each cardiac phase across the cardiac cycle. Flows of all the main renal arteries (left and right and eventually multiple codominant arteries on one side) were added and considered to represent the total RBF.

Renal volumes were calculated with the voxel count method applied to the coronal MR images. For this method, the kidneys were segmented by manually tracing the boundaries of the kidney on each section. [14] The total renal volume was then calculated automatically by adding all voxel volumes lying within the boundaries of the kidney.

Evaluation of images

Based on the phase images, the flow measurements were evaluated qualitatively during a consensus reading by two experienced observers. The flow measurements were considered unsuccessful when they met any of the following criteria: indistinct vessel contour (blurred as a result of motion), wrongly encoded (eg, aliasing, noise), artifacts in the vessel area, ghosting, nonphysiologic or heterogeneous measurement, or signal voids close to the vessel area.

Data analysis

An analysis according to Bland and Altman was performed to assess the degree of direct, short-term and long-term reproducibility of the MR flow measurements. [15] Variability of the measurements was assessed by means of scatter plots showing the difference between two measurements (y-axis) against their mean (x-axis), and by calculating the coefficient of variation (CV) for each parameter. The CV describes the difference as a percentage of the pooled

mean values: (SD of the mean difference/ $\sqrt{2}$) times 100 divided by the pooled mean values. Reproducibility data are shown for the sum of the renal arteries as well as for only the right or left side. The normal values variables were expressed as means with SDs.

Results

The 20 healthy subjects participating in the direct and short-term reproducibility study had a total of 42 renal arteries. Two of the subjects had two codominant renal arteries on one side. None of the subjects had a stenosis of the renal artery. According to the criteria described earlier, 19 measurements were excluded in the direct and short-term reproducibility study (19 of the 3 repeated measurements of 42 renal arteries, 15%). The flow measurements performed in the aorta during the direct reproducibility study had a 100% success rate. In the long-term reproducibility study one of the 19 subjects had a codominant renal artery. Seventeen measurements were excluded because they were qualitatively not suitable (17 of the two repeated measurements of 39 renal arteries, 22%). The 40 volunteers participating in the normal value assessment of the renal flow had a total of 86 renal arteries (four multiple arteries on the left side and two on the right). RBF measurements were judged technically unsatisfactory in twenty-four arteries and were excluded from further analysis (28%). Figure 2 illustrates examples of a technically successful (a) and unsuccessful (b) flow measurement.

The data in Table 1 show the direct reproducibility of the RBF measurements. The mean difference and SDs between the first and second measurements was 17 mL/min ± 128 and 51 mL/min ± 181 for the right and left renal arteries, respectively. The mean difference between the first and second total RBF was 54 mL/min ± 260. The data are presented in a Bland and Altman plot in Figure 3. This figure illustrates that there is no systematic difference between the first and the second measurements. The CVs for the direct reproducibility were 16% and 24% for the right and left renal arteries, respectively, and 17% for the total RBF.

The correlation between the total RBF calculated from the sum of the renal artery flow rates and from the aortic flow difference (suprarenal minus infrarenal) was assessed in 20 volunteers (Table 1). Two subjects (no. 9 and 17) were excluded because their superior mesenteric arteries had their origins at the same level as the renal arteries. There was a good correlation between these two measurements, with a Pearson's correlation coefficient 0.72 ($P = 0.002$; Figure 4). Total RBF tended to be slightly higher when measured as the sum of the two renal arteries.

Table 1 also shows the statistics of the short-term reproducibility of the RBF. The mean differences and SDs between the first and third measurements were 32 mL/min ± 180 and 20 mL/min ± 209 for the right and left renal arteries, respectively. CV's were 23% for the right renal artery and 26% for the left renal artery. The mean difference between the first and third total RBF was 74 mL/min, and the SD of the differences 358 mL/min (CV, 23%; Figure 5).

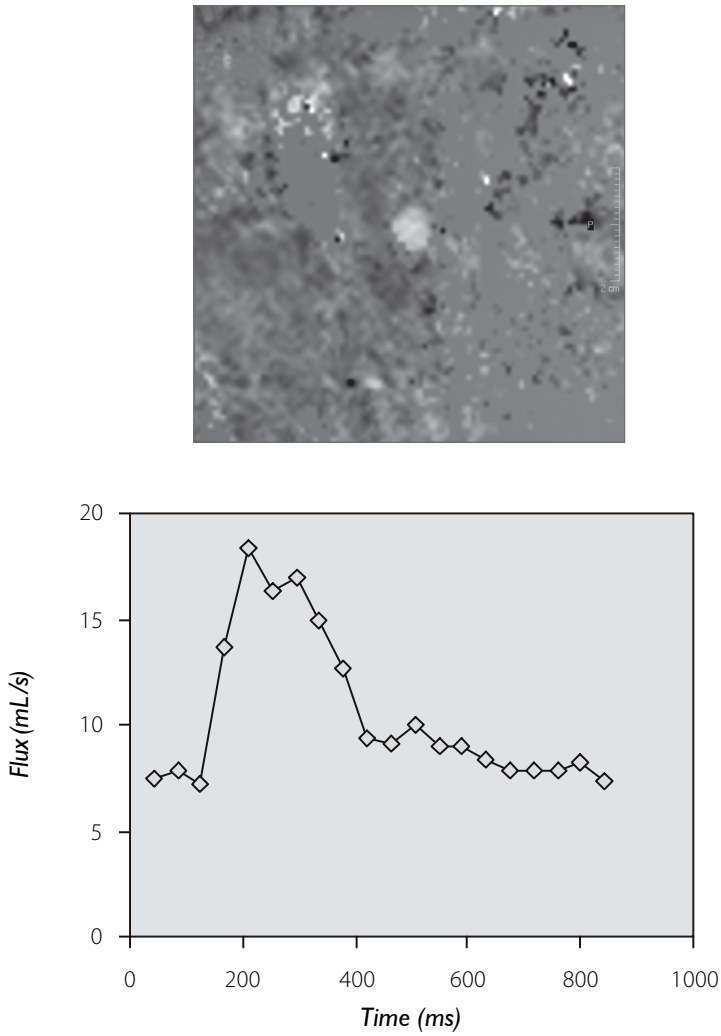

Figure 2a. Cross section through the renal artery in the systolic phase with corresponding flow profile. Illustration of a successful MR flow measurement.

Table 2 shows the statistics of the long-term reproducibility of the RBF. The median time between the two flow measurements was 11 days (interquartile range, 7-21 days). Comparison of the measurements was possible for 11 arteries on the right and 15 arteries on the left side. The mean difference between the two measurements was -8 mL/min, with

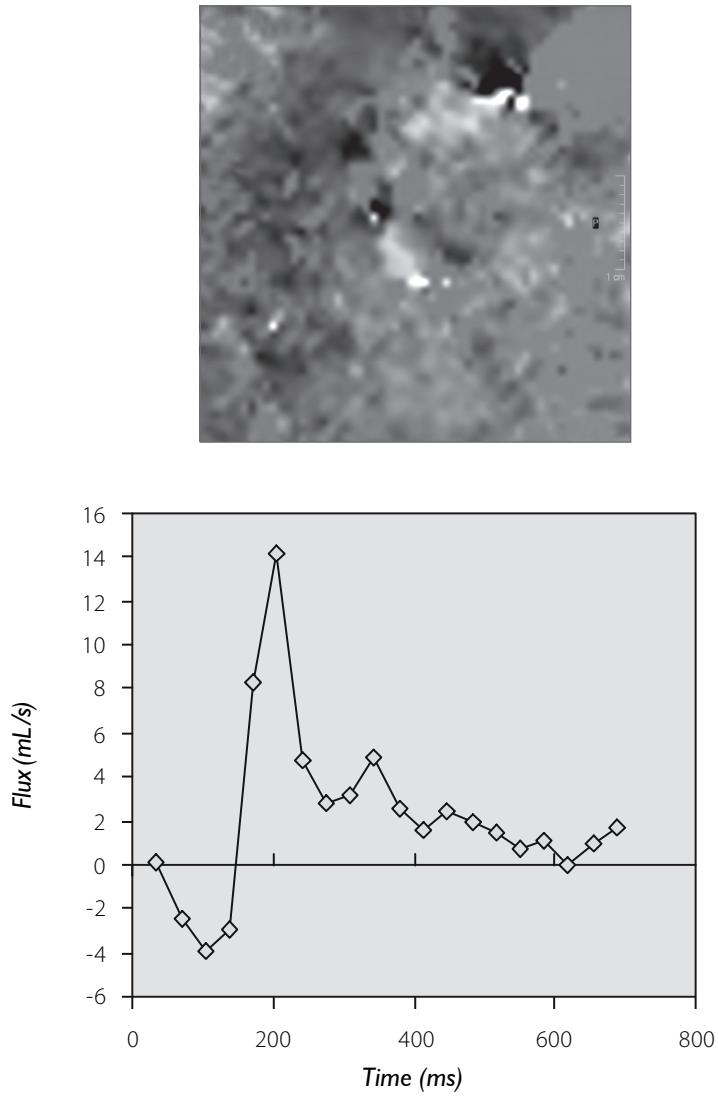

Figure 2b. Cross section through the renal artery in the systolic phase with corresponding flow profile. Illustration of a failed MR flow measurement, the many artifacts make it impossible to recognize the arterial lumen.

SDs of the difference of 170mL/min for the right renal artery (CV, 25%), and 63 mL/min for the left renal artery (SD, 177 mL/min; CV, 26%). The mean difference of the total RBF was 92 mL/min ±279, with a CV of 20%. In Figure 6 the Bland and Altman plot of the measurement at two different points in time is plotted.

Table 1. Measurements of the right, left and total RBF and blood flow rates in the aorta just above and below renal level

Subject	Age (yr)	First measurement (mL/min)			Second measurement (mL/min)			Third measurement (mL/min)			Aorta (mL/min)		
		Right	Left	Total	Right	Left	Total	Right	Left	Total	Suprarenal	Infrarenal	Difference
1	30	619	496	1115	496	600	1096	535	242	777	2401	1483	917
2	32	819	650	1469	549	93	642	-	882	-	4295	1943	2352
3	28	395	355	750	351	316	667	541	472	1013	2406	1732	674
4	27	580	653	1233	693	739	1432	418	546	964	3030	1643	1387
5	28	630	480	1110	755	431	1186	643	426	1068	3106	2162	943
6	29	644	725	1369	517	688	1205	425	428	853	2703	1575	1128
7	26	549	340	889	507	669	1176	402	-	-	3099	2193	906
8	28	550	523	1073	427	475	902	495	809	1304	2194	1261	933
9	29	495	585	1080	596	388	984	699	556	1255	4097	1463	2634
10	26	435	461	897	553	406	959	188	435	623	2224	1395	829
11	24	-	492	-	-	-	-	-	486	-	3721	3198	523
12	27	398	821	1219	583	681	1264	539	620	1160	3564	3011	553
13	30	996	734	1730	974	602	1576	563	336	899	4080	2571	1509
14	27	482	364	846	358	-	-	688	-	-	2531	1983	548
15	28	479	621	1100	569	602	1171	577	907	1484	2129	1088	1041
16	30	-	372	-	682	298	980	-	-	-	2850	1600	1250
17	27	596	622	1218	623	-	-	613	635	1248	5475	2928	2547
18	30	644	-	-	468	-	-	625	637	1262	2679	1544	1135
19	51	812	623	1435	-	614	-	655	-	-	5649	4402	1247
20	29	376	362	739	372	388	760	529	496	1025	2210	1557	653
Mean	29	583	541	1133	560	499	1067	537	557	1067	3222	2037	1029
SD	5	164	145	268	154	178	264	127	186	235	1047	817	440
Minimum	24	376	340	739	351	93	642	188	242	623	2129	1087	523
Maximum	51	996	821	1730	974	739	1576	699	907	1484	5649	4402	2352

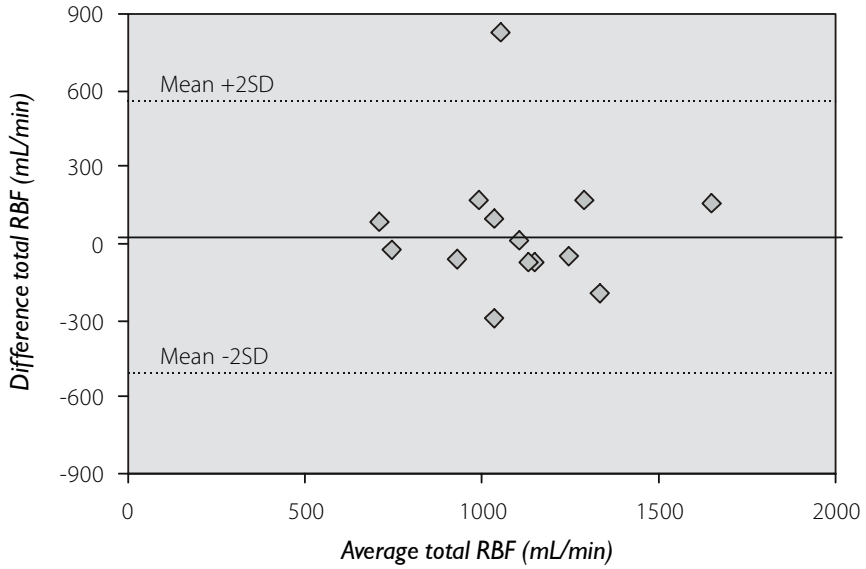

Figure 3. Bland and Altman plot of the first and second total RBF measurements.

Normal values for different age groups were determined in 40 healthy subjects (Table 3). The kidneys were evaluated and judged normal (there were no shriveled kidneys). The mean total RBF was 838 mL/min ± 244. There was a strong relationship between age and total RBF (Figure 7). Men had a higher total RBF than women in the younger age groups, but not after age 60. There seems to be no difference in RBF to the right or left kidney. Total renal volumes and renal function also decreased with age (Table 3). Total RBF increased with creatinine clearance (regression coefficient ß, 8.5 mL/min; 95% CI 4.6-12.3 mL/min) and also increased with renal volume (ß, 2 mL/min; 95% CI, 0.9-2.9 mL/min).

Discussion

This study illustrates that measurement of blood flow in the renal artery by PC MR imaging does not always result in interpretable images. Fifteen to 22% of the measurements in the renal arteries were lost, whereas the aortic flow measurements had a 100% success rate. Although MRI promises to be a minimally invasive technique to assess functional information of arterial RBF, the reproducibility of these measurements is limited. For the direct reproducibility of total renal blood flow the coefficient of variation was 17%, but moving the subject out of the gantry and repeating the measurement after replanning the scan showed modest reproducibility (CV, 23%).

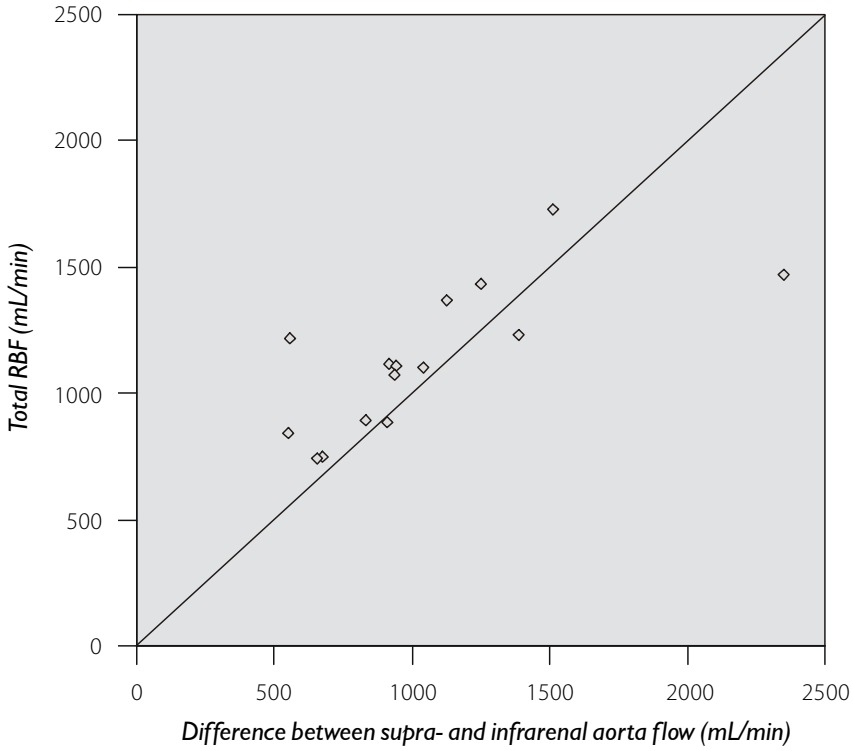

Figure 4. Scatter plot of the difference between the supra- and infrarenal aortic flow and the total RBF. The drawn diagonal represents perfect correlation.

The difficulties in measuring the RBF have been obvious during the development of MR imaging techniques for this purpose. In this study, we have encountered some of these difficulties, which need to be addressed. Motion is the most important one. The kidneys move significantly during breathing and it was demonstrated that the renal arteries show substantial translational motion due to pulsations of blood pressure, ranging from 1 to 4 mm. [16,17] Our scanning protocol was carefully developed consulting recent literature from specialized centers. [5,6] The extra oblique plane through the renal arteries permitted optimal perpendicular positioning for the flow measurement. Some studies have used respiratory gating or breath-hold techniques to cope with the motion of the renal artery, but they have already been abandoned by most of the researchers. [5,6,9,18] Breath-hold techniques allow only limited temporal resolution, which is inappropriate for hemodynamic analysis of the renal artery flow. [13] The vasoreactive trigger of breath holding might furthermore affect

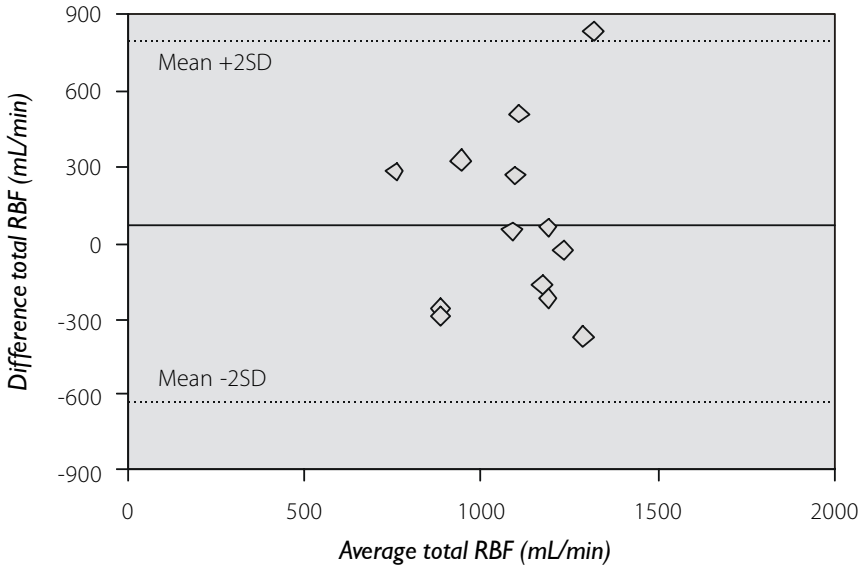

Figure 5. Bland and Altman plot of the first and third total RBF measurements.

RBF quantification. Flow measurement during continuous (shallow) breathing permits longer data acquisition, but results in blurring of the vessel area and makes exact flow quantification difficult (Figure 2). Another explanation for measurement failure may lay in the fact that the blood flow is preferably measured near the ostium, which is often curved in renal arteries. This implies that positioning of the scan plane needs to be more precise, in an artery of relatively small caliber. We furthermore conceived that measurement might fail more often in subjects with higher cardiac frequencies, but such an effect could not be detected (data not shown). The median heart rate in our study population was 62 bpm (with a narrow range from 47-83 bpm).

Success rates of RBF have not been reported before to our knowledge. Many studies have focused on the feasibility to measure the blood flow with PC MR imaging, but little attention has been paid to the reproducibility of this method. [19-21] In fact, there are two studies where the main objective was to assess the reproducibility of RBF measurements with PC MR imaging. In 1992, Sommer et al. established a coefficient of variation of 4.8% for arterial flow measurements repeated after removing the subjects from the scanner in the same session. [19] Although the degree of reproducibility was high, the arterial flow measurements with MR imaging did not correlate well with the corresponding flow determined by the

Table 2. First and repeat measurements of right, left and total RBF after a median of 11 days

Subject	Age (yr)	First measurement (mL/min)			Second measurement (mL/min)		
		Right	Left	Total	Right	Left	Total
1	64	268	313	581	328	202	530
2	27	580	653	1233	618	464	1082
3	45	326	469	794	434	456	890
4	29	644	725	1369	355	479	834
5	44	-	-	-	357	510	867
6	28	550	523	1073	554	678	1232
7	56	442	332	775	556	230	785
8	26	435	461	897	459	659	1118
9	40	-	446	-	-	522	-
10	27	398	821	1219	357	382	740
11	57	-	-	-	-	-	-
12	27	482	364	846	-	525	-
13	65	350	595	945	-	-	-
14	30	-	372	-	525	481	1007
15	59	681	448	1129	-	-	-
16	51	812	623	1435	-	435	-
17	49	425	661	1086	458	565	1023
18	29	376	362	739	692	270	962
19	32	819	650	1469	545	483	1028
Mean	41	506	519	1039	480	459	931
SD	14	170	152	271	113	135	184
Minimum	26	268	313	581	328	202	530
Maximum	65	819	821	1469	692	678	1232

reference, the p-aminohippurate (PAH) clearance. In a more recent report, de Haan et al. assessed the reproducibility of respiratory controlled PC MR flow measurements. [9] The measurements were repeated during the same session, within 5 minutes, without moving the subjects, and without changing the scan parameters. The flow measurements showed good reproducibilities with Pearson correlation coefficients of 0.92 and 0.91. In the present study, the direct reproducibility of measurements was also good. Supposing the flow has a

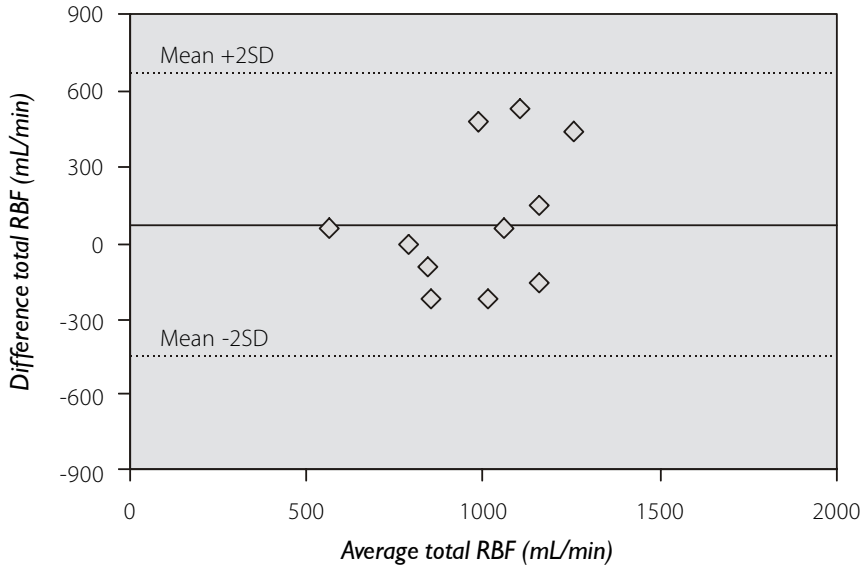

Figure 6. Bland and Altman plot for total RBF measurements repeated after at least 1 week.

hemodynamic steady state, this effect represents the error of the measurement. Moving the subject and planning a new scan in the same session however revealed a lesser degree of reproducibility. The subject variation of the measurement could play a role and the short-term variation is attributable to error in the MR technique as well as the subject variation. Assessment of the long-term reproducibility mainly illustrates physiologic changes in subjects as well as machine error.

In this study we found a good agreement between the measurement of the total RBF and the difference in aortic flow above and below renal level (Figure 4). The flow measurements in the aorta are generally easier to obtain and more reliable than in the renal artery. There are several potential explanations why flow measurement in the aorta was more successful than in the renal artery. First, the diameter of the aorta is significantly larger than that of the renal artery, allowing a better detection and easier planning of the flow measurement. The geometry of the renal artery is more complex, making flow measurement more difficult. Second, the aorta shows limited motion during breathing as compared with the renal arteries. The renal arteries were demonstrated to move mostly in a craniocaudal direction, but not in anteroposterior or right/left direction. [17] Aortic motion in this craniocaudal direction would hardly affect a perpendicular flow measurement, since it is a longitudinal tube. Third, the flow measurements in the renal artery are more sensitive to blurring of the vessel contour as a result of respiratory motion, which can be interpreted as a partial volume effect. As described by Wolf et al., partial volume causes

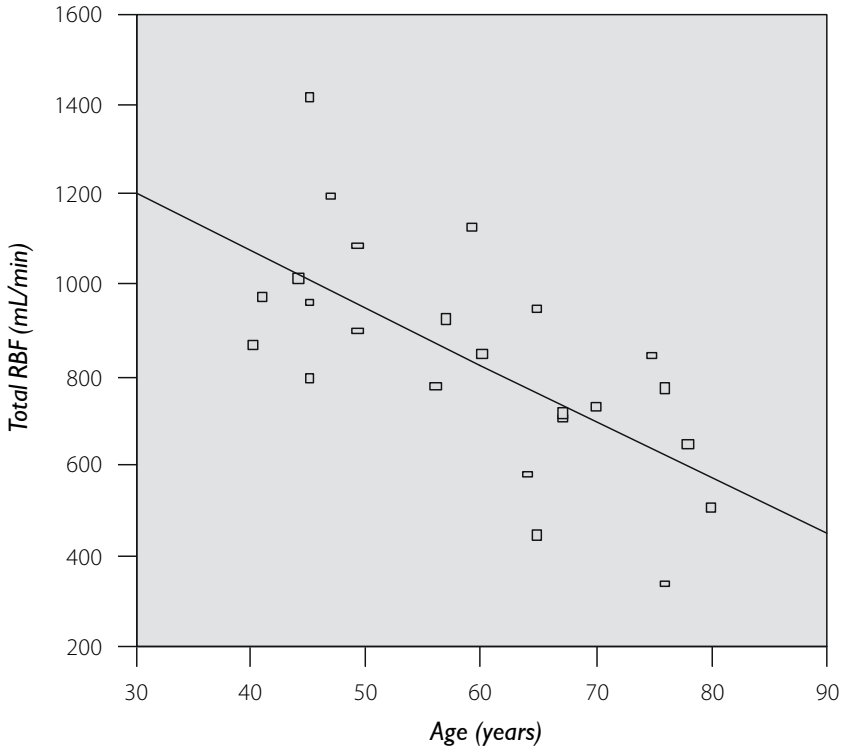

Figure 7. Scatter plot of total RBF versus age. The regression coefficient ß is -12 (95% CI, -19 to -6), meaning that total RBF decreases by a mean of 120 mL/min per decade after age 40.

systematic overestimation of the flow measurement, especially when the lumen of the artery is covered by a limited number of pixels (smaller arteries). [22] This explains the more successful measurement in the aorta. This phenomenon furthermore explains the slightly higher (overestimated) total RBF calculated by the sum of the flow in the renal artery compared with the difference in aortic measurement. A good correlation between the aortic flow difference and total RBF implies that the RBF measurements can be considered valid, which is in accordance with previous reports. [9,23]

Together, the kidneys receive a renal blood flow of 1000 mL/min, which is 20% of the cardiac output. After age 40, the RBF decreases approximately 10% per decade, and renal size also decreases significantly, which is supported by our findings. [24,25]

Several other techniques have been used to measure RBF. Ultrasonography (US) is an easily available, safe and noninvasive method to study the kidneys with low cost. Duplex US also allows acquisition of flow velocity profiles, providing anatomical and functional information. However, US performance is highly dependent on patient morphology and operator skills.

Table 3. Characteristics of the 40 healthy volunteers

	Age 40-50 years		Age 50-60 years		Age 60-70 years		Age >70 years	
	Men (n = 6)	Women (n = 7)	Men (n = 4)	Women (n = 4)	Men (n = 4)	Women (n = 7)	Men (n = 5)	Women (n = 4)
Age (y)	46 ± 3	43 ± 3	57 ± 2	56 ± 1	66 ± 1	64 ± 3	76 ± 4	74 ± 3
Creatinine clearance (mL/min/1.73m^2)	99 ± 11	90 ± 9	86 ±5	80 ± 17	66 ± 5	64 ± 9	55 ± 6	64 ± 10
Renal blood flow (mL/min)								
Right	515 ± 154	446 ± 138	681*	445 ± 84	390 ± 164	368 ± 91	355 ± 65	305 ± 128
Left	571 ± 95	413 ± 79	448*	502 ± 149	281 ± 168	416 ± 126	300 ± 154	341 ± 110
Total	1112 ± 204	910 ± 97	1129*	849 ± 106	576 ± 182	772 ± 158	639 ± 133	637 ± 265
Renal volume (mL)								
Right	192 ± 31	152 ± 20	189 ± 13	152 ± 36	172 ± 22	128 ± 45	161 ± 25	130 ± 25
Left	200 ± 31	170 ± 20	199 ± 17	160 ± 38	177 ± 28	130 ± 29	172 ± 23	132 ± 15
Total	392 ± 61	321 ± 35	388 ± 27	312 ± 72	349 ± 45	258 ± 74	332 ± 46	262 ± 40

Values are means ± standard deviation.

* Based on one flow measurement only, therefore SD is not mentioned.

Recent reports concluded that duplex US is not generally applicable as a screening tool for assessment of renovascular disease. [26,27] RBF can also be measured by Doppler flow wire. The most important advantage of RBF assessment by means of Doppler flow wire is its combination with quantitative renal arteriography. [28] However, a major drawback is that it is an invasive method, making it highly unsuited as a screening test. The use of Doppler flow wire should therefore be limited to guide endovascular intervention.

Our study shows that the quantitative assessment of renal artery blood flow with PC MR imaging has a success rate of at least 75%. The demonstrated internal reliability of this method and fair reproducibility of the flow parameters is crucial for further studies of the renal artery by MR imaging, as a major indication of MR flow measurements will be to detect hemodynamically significant stenoses and potentially predict which patients with renovascular disease are likely to respond to revascularization therapy.

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Chapter 5

Repeat intervention for in-stent restenosis of the renal arteries

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J Vasc Interv Radiol 2002; 13(12):1219-24

Abstract

Purpose

To assess the long-term technical success of repeat endovascular intervention in stenosed renal artery stents.

Materials and methods

Fifteen patients with stenoses ≥50% in a renal stent placed because of an ostial atherosclerotic renal artery stenosis were included in this study. In the presence of increased blood pressure or decreased renal function, the in-stent restenosis was treated with percutaneous transluminal angioplasty (PTA) in the stent or placement of a second stent if the stenosis was located too distally in the stent. The results of these repeat interventions were evaluated by angiography.

Results

The 15 patients had a total of 20 stenosed stents. Eighteen of these in-stent stenoses were treated with PTA and two were treated with placement of a second stent. Angiographic follow-up was available in 16 arteries, showing in-stent restenosis in four (25%; mean follow-up, 11 mo). The cumulative patency rates after repeat endoluminal intervention were 93% (95% CI 80-106) and 76% (95% CI 52-101) after 6 and 12 months, respectively. Renal function remained stable or improved in most patients (80%) after repeat intervention in the stent and hypertension was classified as improved or cured in 47% of patients after one year.

Conclusion

Patients with stenosed renal artery stents can be treated successfully with PTA in a majority of cases, with a long-term success rate of 75% and stable renal function one year after repeat intervention.

Introduction

Atherosclerotic renal artery stenosis is associated with increased blood pressure and renal insufficiency. The stenosis is frequently located in the ostium of the renal artery. In the last few years, stent placement has become the treatment of choice instead of percutaneous transluminal renal angioplasty. [1]

Reports of the direct technical success rate of stent placement for renal artery stenosis are abundant. Immediate revascularization success rates in patients with ostial lesions range from 96% to 100%, but stenosis in the stent was diagnosed in 11%-39% of cases within one year of follow-up. [2-7] The stenosis in the stent is often caused by myointimal hyperplasia. [2,6] When this in-stent stenosis occurs, it is generally treated with percutaneous transluminal angioplasty (PTA) and/or placement of a second stent. [1,2,4,6,8,9] The direct technical success rate of the repeat interventions is usually high; however, the long-term effects are yet to be determined. The aim of this study was to assess prospectively the long-term technical success rate of repeat endovascular intervention of stenoses in renal artery stents.

Materials and Methods

Patients

From September 1992 to August 1997, all patients who presented with an angiographically proven in-stent restenosis that required treatment were enrolled in this study (n = 15). Stenosis in the stent was defined as reduction of 50% or more in luminal diameter of the stent. The stenosis in the stent was diagnosed during routine angiographic follow-up after the initial stent placement procedure or during an earlier angiography procedure for in-stent stenosis suspected on clinical grounds. Clinical indication for angiography included an increase in diastolic blood pressure of at least 15 mmHg without a change in antihypertensive medication regimen or an increase in plasma creatinine level of at least 20% that developed spontaneously or after the start of treatment with angiotensin-converting enzyme (ACE) inhibitors. Details of initial stent placement and follow-up have been described elsewhere. [1,7,10] Informed consent was obtained and the study was approved by the hospital's medical ethics review committee.

In-stent intervention

As mentioned before, a stenosis in the stent was defined as a reduction of 50% or more in luminal diameter in the stent, with the diameter of the first normal segment distal to the stent used for reference. In the presence of clinical symptoms such as hypertension and/or deterioration of renal function, the in-stent stenosis was treated with angioplasty in the stent; in the case of a stenosis located distally in the stent, a second stent was placed. Patients

without symptoms were left untreated. For treatment of in-stent stenosis with PTA, the balloon was positioned within the stent and subsequently inflated at a pressure of 5 atm. The balloons used for in-stent treatment were similar to the ones used for regular PTA in the renal artery. Lesions situated in the distal part of the stent were treated with a stent crimped on a PTA balloon which was deployed in part within the first stent. The stents used in this study were all Palmaz stents. The stents measured 1 cm, 1.5 cm, and 2 cm in length and were dilated to diameters of 4-9 mm. The pharmacologic regimen used for repeat intervention for in-stent stenosis consisted of intravenous heparin (5,000 IU) during the procedure. Treatment was continued with orally administered warfarin until adequate anticoagulation was achieved. After 3 months, warfarin was replaced by aspirin (100 mg/d). In March 1997, warfarin was deleted from the regimen and patients received only 100 mg of aspirin daily, starting the day before the procedure, with heparin administration during the procedure. The intervention was judged technically successful if the residual stenosis in the stent was less than 50% of the luminal diameter at the end of the procedure.

Angiographic and clinical follow-up after repeat intervention

All patients were followed clinically. Renal function, blood pressure, and antihypertensive medication were registered before, immediately after, and 1, 3, 6, and 12 months after intervention in the stent. Direct and long-term clinical success was classified according to Society of Cardiovascular and Interventional Radiology guidelines. [11] Cure of hypertension is defined as diastolic blood pressure ≤90 mmHg without antihypertensive medication. Improvement is defined as a diastolic blood pressure ≤90 mmHg or a reduction of at least 15 mmHg during administration of equal or less antihypertensive medication. Any other result is considered a failure. Improvement in renal function is defined as a decrease of at least 20% in plasma creatinine level; worsening is defined as an increase of at least 20%. Any other result is defined as unchanged renal function.

After 12 months, angiographic control images of the in-stent intervention were obtained in all patients. Angiography was repeated earlier if recurrent in-stent stenosis was suspected on clinical grounds (increase in diastolic blood pressure of at least 15 mmHg during unchanged antihypertensive medication or increase in plasma creatinine level of at least 20% that developed spontaneously or after the start of treatment with ACE inhibitors). If cholesterol embolism had occurred in previous angiographic procedures, computed tomographic (CT) angiography was performed instead of angiography. The angiograms were assessed in consensus reading by two experienced vascular radiologists.

Table 1. Baseline characteristics of the study population

Characteristics	n = 15
Mean age (yr) ± SD	62 ± 9
No. of male pts.	9 (60)
Type of stenosis / stent placement	
Unilateral	5 (33)
Bilateral	7 (47)
Unilateral stenosis with contralateral occlusion	3 (20)
Mean follow-up at first recurrence (mo) ± SD	13 ± 12

Values in parenthesis are percentages.

Statistical analysis

Continuous variables were expressed as means ± SD. The cumulative patency rate after intervention in the stent curve was obtained with use of the Kaplan-Meier method. Because of our primary interest in the technical success of endovascular treatment of in-stent stenosis, we performed survival analysis of patency after intervention in the stenotic stent on a per-artery basis, not a per-patient basis. Differences in renal function and blood pressure before intervention and after 1 year of follow-up were determined with use of a paired-samples *t* test. Statistical analysis was completed with use of SPSS statistical software (SPSS, Chicago, IL). A *P* value less than 0.05 was considered statistically significant.

Results

In-stent stenosis

In-stent restenosis in the 15 patients in this study was diagnosed at a mean follow-up of 13 months after initial stent placement (range, 2-46 mo). All restenoses were detected by angiography because none of the patients had experienced cholesterol embolism previously. The baseline characteristics of these patients are listed in Table 1.

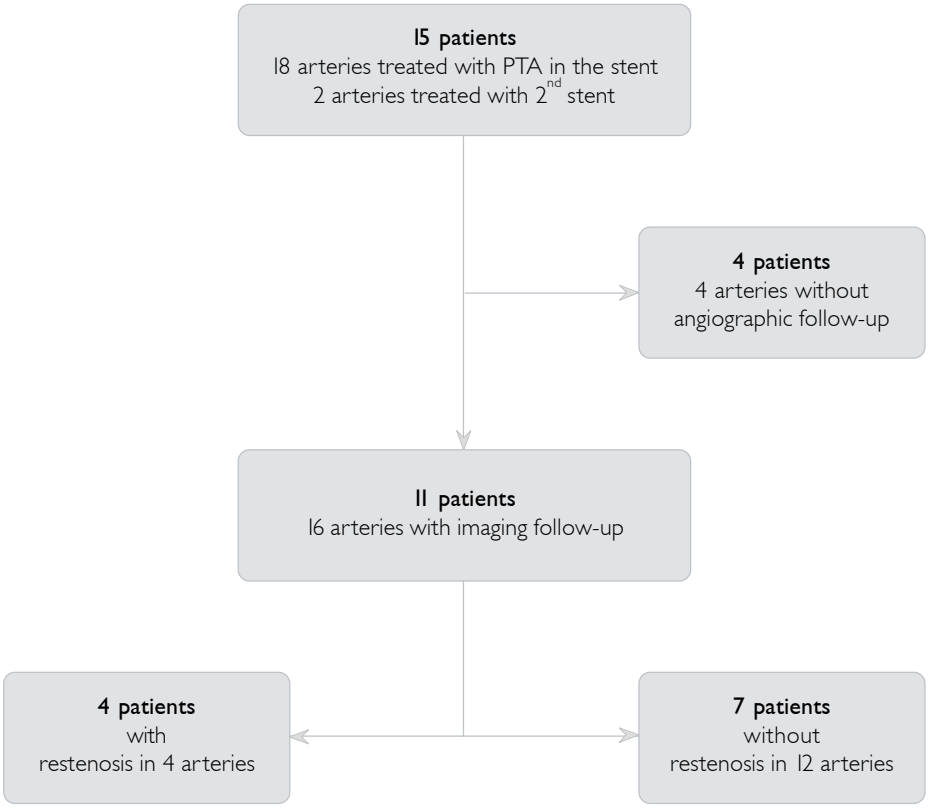
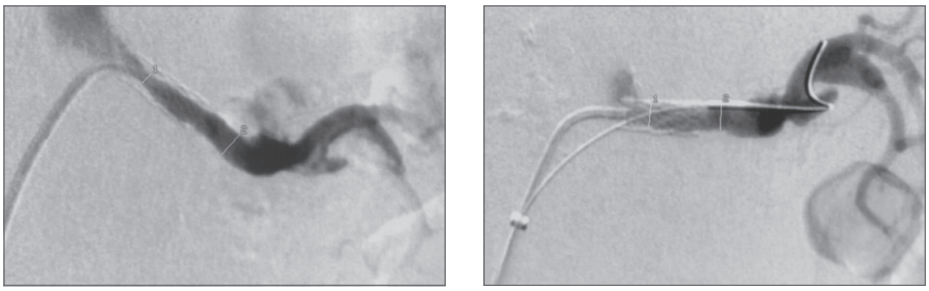


Figure 1. Follow-up after repeat intervention for in-stent restenosis.

Intervention and follow-up

The 15 study patients had 23 arteries in which 24 stents were placed (two stents were placed in one artery in one case). In one patient, stents were placed in both stenosed arteries on the same side. Restenosis in the stent occurred in 20 of the 23 arteries in these 15 patients. Eighteen arteries were treated with PTA in the stent and two were treated with placement of a second stent. All PTA interventions and second stent placements were technically successful, leaving a residual stenosis of less than 50%. The results are schematically shown in Figure 1. Figure 2a illustrates a stenosed renal artery stent that was subsequently dilated with balloon angioplasty in the stent (Fig 2b).



a b

Figure 2. Selective digital subtraction angiography of the renal artery. **(a)** Left renal artery presenting with an in-stent stenosis 6 months after initial stent placement. **(b)** The stenosis was subsequently dilated with balloon angioplasty in the stent, leaving a residual stenosis of approximately 10%.

Imaging follow-up of the in-stent intervention in these 20 arteries (15 patients) was available in 16 arteries (11 patients; mean follow-up, 11 months after repeat intervention; range, 4-38 mo). In two patients, we refrained from performing angiography one year after repeat intervention because of complications after the previous angiography procedure. Angiography was not performed in another patient because of a cerebral vascular accident. One other patient refused to undergo angiography because of a lack of symptoms. Follow-up was performed by angiography in all but one patient, in whom the risk of cholesterol embolism was considered high because of a rapidly growing thoracoabdominal aneurysm, and therefore CT angiography was performed. Four arteries (in four patients) were found to have a recurrent stenosis in the stent that required further treatment. PTA was performed in three arteries; a stent was placed in one. These procedures were also technically successful, leaving a residual stenosis of less than 50% in all stents. The other 12 arteries had no restenosis in the stent (12 of 16 = 75% patent stents). Figure 3 shows the cumulative patency in the stents after intervention was performed because of in-stent stenosis. The patency rates after repeat endovascular intervention were 93% (95% CI 80-106) and 76% (95% CI 52-101) after 6 and 12 months, respectively.

In all patients, clinical findings were available immediately after the procedure in the stent and at 12 months follow-up. Table 2 illustrates the effect of in-stent intervention on renal function and hypertension. Renal function remained stable in most patients and hypertension was classified as improved in 40% of patients after 1 year. The mean systolic and diastolic blood pressures were lower 1 year after the intervention than before intervention, but the difference did not reach significance (Table 2).

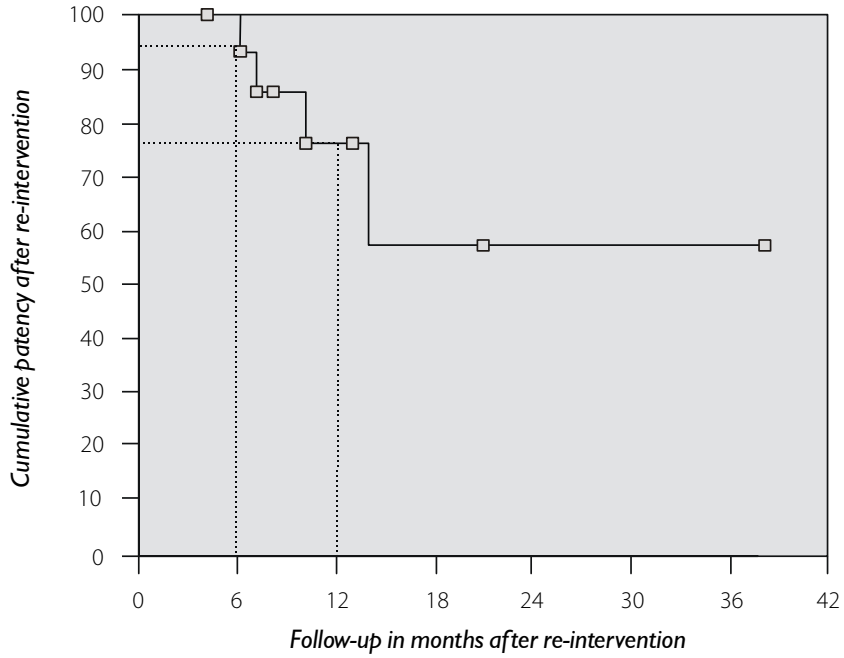


Figure 3. Cumulative patency of the arteries after repeat intervention in the stents because of restenosis.

Complications of repeat in-stent intervention

Nephrectomy was performed in one patient shortly after stent placement for in-stent restenosis. The initial stent placement procedure had been complicated by a dissection of the renal artery. During the first follow-up angiography procedure, a false aneurysm that had developed distal to the stent was treated together with the in-stent stenosis by placement of a second stent. Although the procedure was technically successful, the kidney could not be saved. In one other patient, the in-stent PTA procedure was complicated by pulmonary overfilling caused by contrast material-induced nephropathy. The patient was treated successfully with diuretics and restoration of the serum creatinine level was achieved. None of the procedures were complicated by cholesterol embolism and there were no deaths during follow-up.

Table 2. Clinical outcomes directly after and 12 months after intervention in the stent (n = 15)

Outcome category	Before intervention	Directly after intervention	12 months after intervention	P Value*
Renal function				
Mean serum creatinine level (μmol/L) ± SD	172 ± 65	169 ± 68	163 ± 61	0.4
Improvement	-	1 (7)	2 (13)	
Unchanged	-	13 (87)	10 (67)	
Worsening	-	1 (7)	3 (20)	
Hypertension				
Mean systolic blood pressure (mmHg) ± SD	173 ± 35	146 ± 18	156 ± 30	0.055
Mean diastolic blood pressure (mmHg) ± SD	94 ± 17	83 ± 12	81 ± 26	0.063
Cure	-	1 (7)	1 (7)	
Improvement	-	13 (87)	6 (40)	
Failure	-	1 (7)	8 (53)	

Values are presented as numbers of patients with percentages in parenthesis unless otherwise specified.
* Comparison of renal function and blood pressure before intervention versus 12 months after intervention.

Discussion

In this study, we demonstrated that in-stent restenoses of the renal artery can successfully be treated with PTA in the stent or placement of a second stent. The direct technical success rate of this repeat intervention was excellent; a residual stenosis of less than 50% was achieved in all patients. The long-term technical success rate after a mean of 11 months of follow-up was 75%.

In the literature, in-stent stenosis rates range from 11% to 39% from 6 to 12 months after stent placement. [1-6] Rates were higher in older patients with more severe atherosclerosis and depended on the type of stenosis treated. In-stent stenosis was more prevalent in ostial stent placement procedures. Stenoses in stents are usually treated with intrastent PTA or placement of a second stent. [2,6,9,12-14] A few studies also reported the use of excimer laser-

assisted angioplasty, rotational atherectomy, and surgical end-atherectomy. [4,14] Most studies of the long-term effects of stent placement simply state the in-stent stenosis rate and report its immediate technically successful treatment; only one author reported on the follow-up of repeat intervention in the stent. [8] Hennequin et al. were able to follow two of the three patients who had PTA in the stent for local in-stent stenosis by angiography. [8] In the first patient, patency was maintained 7 months after the in-stent intervention. In the second patient, the performance of a second PTA procedure in the stent was necessary 10 months after the first repeat intervention. In the present study, follow-up imaging after repeat intervention was performed in 11 patients after a mean of 11 months, 10 of 11 by angiography. By survival analysis, we found a 76% cumulative patency rate of the stent 1 year after repeat intervention. However, this result can be used only as an indication of the patency achieved by in-stent repeat intervention. The confidence intervals are large and therefore these results should be interpreted with care.

Treatment and follow-up of in-stent stenosis have been thoroughly described in coronary artery studies. The coronary stenoses are much more prevalent than the renovascular ones, thereby providing larger study populations. Stent placement is increasingly used as the first choice of treatment in patients with coronary artery disease. Coronary in-stent stenosis rates range from 15% to 35% after initial stent placement. [15-17] Long-term outcomes of balloon angioplasty in the stent and placement of a second stent seem clinically favorable, but the angiographic recurrence rate of in-stent stenosis is high, ranging from 22% to 54% after 6 months. [15-17] However, these repeat interventions are considered safe and immediately technically effective. These results show that in-stent stenosis occurs frequently and that, although the direct effects are favorable, recurrence of in-stent stenosis is prevalent.

In this study, we demonstrated that the clinical outcomes of treatment in the renal artery stent were good. In 80% of the patients, the serum creatinine level remained stable or improved. Atherosclerotic renovascular renal failure is a progressive disorder and prevention of deterioration in renal function is an important outcome for these patients. [18-19] The immediate effect of in-stent repeat intervention on blood pressure was good, with improvement or cure of hypertension achieved in almost 90% of patients. One year after the repeat intervention, most of this effect subsided, leaving only approximately 50% of patients with successfully controlled blood pressure. This is in line with a recent study that showed that revascularization has a modest effect on blood pressure. [20] This is a common finding and therefore the focus of endovascular renal artery treatment has shifted from hypertension to renal failure. [21]

Angiographic follow-up of our patients was performed one year after repeat intervention in the stent. Angiography is still the standard of reference in assessing patency of the renal artery and renal artery stents and such an accurate measurement is needed in a research setting. [22,23] It offers the further advantage of a direct opportunity for treatment in case of a stenosis. However, angiography is an invasive procedure associated with serious complications, the most important one being cholesterol embolism. This can lead to renal infarction with further deterioration of renal function. Our study demonstrated that 25% of the cases of in-stent restenosis treated by repeat intervention had recurrent restenosis after one year. This affects a considerable number of patients. Follow-up of in-stent repeat interventions is needed, but, in practice, angiography might not be the most clinically useful way to do it. Duplex ultrasonography (US) has emerged as a safe, inexpensive, and sensitive tool to detect restenosis of renal artery stents in a majority of patients. [24] We would recommend that these patients be monitored by US instead of angiography. In cases in which US indicates in-stent restenosis or when renal function deteriorates despite a negative US result for in-stent restenosis, angiography might still be indicated.

Long-term patency of treated renal arteries may be helpful in the preservation of renal function and postponement of end-stage renal disease in patients with atherosclerotic renovascular disease. [10,25] Two limitations of the present study are that not all patients underwent follow-up angiography and that the time between repeat intervention and follow-up was quite variable.

In conclusion, stenosis in stents is frequent and affects a considerable proportion of patients with atherosclerotic ostial renal artery stenosis treated with renal stent placement. In-stent restenosis can successfully be treated by balloon angioplasty in the stent in a majority of patients and has a 75% technical success rate after a mean follow-up of 11 months. Renal function was stable one year after in-stent repeat intervention.

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Part III

Prevention of renal function loss in patients with atherosclerotic renal artery stenosis

Chapter 6

The benefit of STent placement and blood pressure and lipid-lowering for the prevention of progression of renal dysfunction caused by Atherosclerotic ostial stenosis of the Renal artery. The STAR-study: rationale and study design.

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on behalf of the STAR study group

J Nephrol 2003; 16(6):807-12

Abstract

Background

Atherosclerotic renal artery stenosis (ARAS) is associated with progressive loss of renal function and is one of the most important causes of renal failure in the elderly. Current treatment includes restoration of the renal arterial lumen by endovascular stent placement. However, this treatment only affects damage caused by ARAS due to the stenosis and ensuing post-stenotic ischemia. ARAS patients have severe general vascular disease. Atherosclerosis and hypertension can also damage the kidney parenchyma causing renal failure. Medical treatment focuses on the latter. Lipid lowering drugs (statins) could reduce renal failure progression and could reduce the overall high cardiovascular risk. The additional effect on preserving renal function of stent placement as compared to medical therapy alone is unknown. Therefore, the STAR-study aims to compare the effects of renal artery stent placement together with medication vs medication alone on renal function in ARAS patients.

Method

Patients with an ARAS of ≥50% and renal failure (creatinine (Cr) clearance <80 mL/min/1.73 m^2) are randomly assigned to stent placement with medication or to medication alone. Medication consists of statins, anti-hypertensive drugs and antiplatelet therapy. Patients are followed for 2 years with extended follow-up to five years. The primary outcome of this study is a reduction in Cr clearance >20% compared to baseline. This trial will include 140 patients.

Introduction

Atherosclerotic renal artery stenosis (ARAS) is associated with progressive loss of renal function and is one of the most important causes of renal failure in the elderly. [1-3] Traditionally, treatment aims to relieve the stenosis. However, post-stenotic kidney ischemia is only one of the factors playing a role in the pathogenesis of atherosclerotic renovascular renal failure. In fact, the kidney can be affected by the systemic effects of hypertension, atherosclerosis and hyperlipidemia, which induce nephrosclerosis and focal segmental glomerulosclerosis. [4] Cholesterol embolisms are also frequently observed in patients with ARAS causing glomerulosclerosis and renal failure. [4]

Although restoration of the renal arterial lumen is current practice, it is unknown whether it has the additional effect of preserving renal function compared to optimal medical treatment alone. Therefore, this randomized trial is being undertaken. Renal function, complication rates, cardiovascular outcomes, all-cause mortality, quality of life and economic outcomes will be compared for medical therapy alone and medical therapy plus stent placement. We report the study protocol.

Subjects and methods

Study design

This is a randomized, multicenter trial of patients with an ostial ARAS and renal failure. Patients will be randomized to: (i) medical treatment consisting of antihypertensive, lipid-lowering and antiplatelet therapy plus the advice to stop smoking; or (ii) medical treatment as outlined in (i) with additional stent placement. Table 1 depicts eligible patient criteria. The enrolment of 140 patients will take place in 11 centers (nine in the Netherlands, one in France and one in the UK). Randomization started in June 2000 with completion expected in January 2005. There will be a 2-yr follow-up, with an extended follow-up of 5 yrs.

Statistical considerations

Sample size

Based on our own experience and reported findings, we assumed that 50% of medically treated patients would show deteriorating renal function and that this percentage could be reduced to 20% by additional stent placement. With a power of 0.90 and an alpha of 0.05, this reduction in adverse outcomes can be demonstrated in a group of 116 patients. Furthermore, with a sample size of 130 patients a difference in Cr clearance of 15 mL/min (standard deviation (SD) 20 mL/min) can be demonstrated with a power of 0.8 and an alpha of 0.05. Considering an approximate patient dropout-rate of 10%, the sample size was set to 140 patients.

Table 1. Inclusion and exclusion criteria

I. Inclusion criteria
Age > 18 years
Ostial ARAS ≥50% on CTA, MRA or intra-arterial angiography
Estimated Cr clearance <80 mL/min/1.73 m^2 according to the Cockcroft and Gault formula, on two occasions within one mth
II. Exclusion criteria
Declined informed consent
Proven cholesterol embolisation at previous interventions
Renal artery diameter <4 mm
Estimated Cr clearance < 15 mL/min/1.73 m^2
Diabetes mellitus with proteinuria >3 g/24 hr
Any known cause of renal failure other than ischemic nephropathy
Pulmonary edema in the presence of bilateral renovascular disease in combination with intolerance of ACE-inhibitors/ Angiotensin-II antagonists defined as a fall of estimated Cr clearance of >20%
Malignant hypertension (fundus grade III/IV)
Myocardial infarction or CVA <3 months before planned inclusion date
Contra-indication for the use of atorvastatin
- Elevated liver-enzymes (> normal values; AST, ALT, Alk Phos, γGT)
- Elevated CK (>3x normal)
- Known allergy to statins
- The use of erythromycin, gemfibrozil or cyclosporin
- History of alcohol abuse

Randomization

Randomization will be done per center and will be stratified for unilateral or bilateral ostial renal artery stenosis. A unilateral stenosis is defined as a unilateral ostial stenosis with a contra-lateral normal renal artery or with a contra-lateral truncal stenosis. All other patients are considered to have bilateral ostial renal artery stenosis. Therefore, this latter group includes patients with bilateral ostial stenosis, patients with a unilateral ostial stenosis and a contra-lateral occlusion and patients with a solitary kidney with an ostial stenosis.

Table 2. Primary and secondary end points

I. Primary end point
Progressive renal function loss (defined as a reduction of estimated Cr clearance by >20%) after 2 yrs follow-up, with an extended follow-up of 5 yrs
II. Secondary outcomes
Acute complications
Late complications
Occlusion of the stenotic renal artery
Incidence and time to doubling of serum Cr
Initiation of dialysis therapy
Effect on hypertension and the occurrence of therapy refractory or malignant hypertension
Incidence of pulmonary edema
Cardiovascular morbidity and mortality
Total mortality
Cost-effectiveness
Quality of life

End points

Table 2 presents the primary and secondary end points. Patients reach a primary end point when their estimated Cr clearance decreases by >20% compared to the baseline value (based on two measurements). In case of recurrent stenosis in the stent group, a primary end point is reached if after in-stent balloon dilatation the >20% reduction in Cr clearance persists. In patients requiring a stent during the trial, further follow-up will be the same as for the primary stented patients.

Patients

Patients with an ostial ARAS, a Cr clearance of <80 mL/min/1.73 m^2 according to the Cockcroft and Gault formula and stable blood pressure (BP) control are enrolled in this trial. Ostial ARAS is defined as a luminal reduction of ≥50% of the renal artery within 1 cm of the aortic wall, in the presence of atherosclerotic changes of the aorta. Stenosis evaluation can be performed on CT-angiography, MR-angiography or intra-arterial angiography. Two experienced radiologists at the coordination center in Utrecht will evaluate all angiograms.

The mean of two fasting serum Cr values determined within 1 month is used to assess the baseline renal function. The patients are required to have stable BP control, preferably in the absence of ACE-inhibitors or Angiotensin-II antagonists. Compelling indications to introduce or continue the use of these drugs include heart failure, renovascular pulmonary edema and post-myocardial infarction.

Study plan

Medical therapy

Irrespective of baseline serum cholesterol values, the patients will be treated with lipid lowering therapy: 10 mg of atorvastatin and if this is well tolerated the dose will be doubled to the final dose of 20 mg. Any lipid-lowering medication currently used is discontinued and replaced by atorvastatin. The statin will be stopped if there is an increase of creatine kinase (CK; > 10-fold normal) or an increase in liver-enzymes (>3x normal). After laboratory test result normalization, the statin will be re-instituted in half the original dose. Hypertension is treated with the following drugs: thiazide diuretic, calcium antagonist, beta-blocker and alpha-blocker. ACE-inhibitors/Angiotensin-II antagonists together with increasing loop diuretics doses, should be used only as last resort antihypertensive treatment when other classes of antihypertensive agents have failed. The target BP is < 140/90 mmHg. Patients will receive antiplatelet therapy, aspirin 75-100 mg/od. Considering that smoking is a major renal risk factor, smokers will be advised to stop.

Stent and medical therapy

Medical therapy is identical in the two treatment arms. In the stent group, patients will start with aspirin 75-100 mg/od the day before admission. The stent (Palmaz-Corinthian IQ / Palmaz Genesis, Johnson & Johnson Medical NV/SA) will be placed during an in-patient admission according to a standardised protocol.[5] During the same session, truncal stenoses will be treated by balloon angioplasty.

Follow-up

Clinical follow-up is scheduled after 1, 3 and then every 3 months for the first 2 yrs and every 6 months until the 5 yr follow-up is completed. Fasting serum Cr is measured and recorded at every visit, as well as BP 3x in sitting position. Total cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol and triglycerides will be recorded after 1, 3 and 6 months, then every 6 months for 5 yrs. The liver-enzymes (AST, ALT, AF and γGT) and CK will be recorded after 1, 3, 6 and 12 months, then every 12 months for 5 yrs. Economic data are assessed after 3 months and every 3 months for 2 yrs. Quality of life will be measured by standardized SF-36 and EQ-5D health questionnaires before, after 1 month and every 6 months for 2 yrs.

Indications for angiography

Indications for stent placement in the medically treated patients and re-angiography and balloon dilatation of the stent in the stented patients are:

(i) persistent >20% reduction of Cr clearance

(ii) therapy refractory hypertension (defined as an office BP > 180/100 mmHg during three follow-up visits and subsequently a mean daily BP of > 160/95 mmHg on 24 hr ambulant BP monitoring, while on the maximum dose of all classes of antihypertensives)

(iii) pulmonary edema in the presence of bilateral renovascular disease and a normal or slightly impaired left ventricular function on echocardiography in combination with ACE-inhibitors/Angiotensin-II antagonists intolerance defined as a fall of the estimated Cr clearance by >20%

(iv) malignant hypertension (defined as fundus grade III/IV)

In patients needing ACE-inhibitors (or angiotensin-II antagonist) and having a >20% reduction of their estimated Cr clearance this will be verified by repeat determination 4 wks after the discontinuation of these agents. If the fall in Cr clearance persists, this will be verified after one month. If the patient then has a >20% reduction in Cr clearance, he will be referred for angiography.

Analysis of the results

The difference in the proportion of patients with progressive renal dysfunction between both treatment arms will be assessed including 95% confidence intervals (95% CI). Mean change and difference in renal function change, including 95% CI will be reported. With multivariate logistic regression analysis not only will the effects of the two treatment strategies be evaluated, but also whether there are independent effects of age, smoking, proteinuria, bilateral or unilateral renal artery stenosis, BP and renal function at baseline. The illness free interval will be analysed by a Kaplan-Meyer tabulation and a Cox's regression analysis. Comparable analyses will take place regarding the end point, event free survival, cardiovascular disease manifestations and overall mortality. To estimate the long-term cost-effectiveness and cost-utility a Markov model will be used. Incremental costs per Quality Adjusted Life Year (QALY) gained over the remaining life expectancy will be reported. Analysis will take place according to an intention to treat principle. After inclusion of the first 70 patients an interim analysis will be performed.

Discussion

The factors that play a role in the pathogenesis of atherosclerotic renovascular failure are: (1) ischemia due to hypoperfusion of the post-stenotic kidney; (2) hypertension- and atherosclerosis-induced nephrosclerosis; (3) focal segmental glomerulosclerosis due to hyperlipidemia and atherosclerosis and; (4) cholesterol embolism.

Stent placement

The introduction of intravascular stents in the early 1990s provided a minimally invasive means of achieving excellent and long-term patency of the treated renal artery. Stent placement is technically successful in 98% of the patients and compared to percutaneous transluminal angioplasty, it has considerably lower recurrence rates (17% vs. 26%). [6] Renal perfusion restoration by stent placement has yielded reasonably good clinical outcomes with improvement of hypertension and the reduction in renal failure progression rate. [2,7] There are a few studies that primarily investigated the effect of renal artery stenting in renal failure patients. [2,7-10] Amelioration or stabilization of renal function was achieved in the majority of patients. Patients with a renal function decline before stent placement seemed to benefit more from the intervention than patients with stable renal function. [2,7,10] However, these studies were uncontrolled and some retrospectively designed. [8,9] Therefore, what the renal function course would have been without intervention is unknown. If left untreated, more than half of the ARAS patients show deteriorating renal function during follow-up. [11] In a series of patients with severe renovascular disease treated conservatively, the renal function decline averaged 4 mL/min/yr. [1] However, these patients were selected because the lesions were not amenable to angioplasty, had small kidneys or because the patients were unsuitable for surgical intervention. ARAS treatment in azotemic patients with endovascular stent placement compared to conservative therapy is yet unstudied in a randomized trial. Therefore, this precludes comparison between studies investigating either one of the treatments.

Stent placement procedures are costly and not free of complications. [12] In approximately 5% of the patients, a serious complication occurs that requires intervention and 1% of the stent placements is complicated by loss of renal function and the need for renal replacement therapy. In addition, stent placement mortality is 1%. The ultimate goal of renal artery intervention is to prevent end-stage renal failure. However, in the Harden study, approximately 50% of the stented patients had died before becoming dialysis-dependent. [2] For renal stent therapy to be cost-effective, the gain in terms of renal function must therefore be very pronounced.

Medical treatment

Optimal BP regulation is crucial in the management of patients with renovascular renal failure. Hypertension can cause nephrosclerosis, resulting in renal function loss. However, studies have shown that despite antihypertensive treatment, renal failure was progressive in 38-46% of the patients. [13,14] Nephrosclerosis, which in addition to hypertension, can be caused by ageing and atherosclerosis, can cause renal failure. [15] Therefore, the importance of BP control is evident in this patient group to prevent further nephrosclerosis. Although ACE-inhibitors and angiotensin-II antagonists could have a positive impact on the course of renal function, they are not generally prescribed for fear of reducing renal function and of post-stenotic kidney shrinkage in these patients. [16]

Focal and segmental glomerulosclerosis characterize the histology of atherosclerotic renovascular renal disease. This is often seen in relation to hyperlipidemia and atherosclerosis, but not ischemia. [17-20] In patients with atherosclerotic renovascular disease, the severity of the proximal stenosis often seems unrelated to the severity of renal dysfunction. [19,20] Autopsy studies have shown a significant correlation between the severity of atherosclerosis and the extent of glomerulosclerosis. These findings suggest a close relationship between atherosclerosis risk factors (such as hyperlipidemia) and the development of glomerulosclerosis. [21]

Furthermore, the observation that patients with chronic renal failure and associated proteinuria have a two-fold increase in the progression rate of renal dysfunction if their serum lipid levels are elevated compared to a cohort with normal lipid levels, suggests that hyperlipidemia can accelerate the rate of renal function decline. [22]

Therefore, drugs that focus on lipid-reduction should be considered a part of the therapeutic regimen of ARAS patients. In addition, in different models of progressive renal failure, lipid-lowering HMG-CoA-reductase-inhibitors (statins) have been shown to ameliorate the extent of renal injury and renal failure. [23] *In vitro* and *in vivo* studies demonstrated that statins slow renal failure progression by inhibiting monocyte infiltration, mesangial cell proliferation with mesangial matrix expansion, tubulo-interstitial inflammation and fibrosis. [23] In a recent meta-analysis, Fried et al. demonstrated that lipid reduction may preserve glomerular filtration rate and may reduce proteinuria in patients with renal disease. [24] Statins may also play an important role on the modulation of progressive renal failure by their influence on endothelial dysfunction. [23] In addition, statins might have a beneficial effect on plaque inflammation. Despite the above-mentioned potential effects, the role of statins on atherosclerotic renovascular renal failure has not yet been investigated. The properties of the statins used in patients with renal failure should preferably include an extrarenal excretion, few side-effects and low risk for drug interactions.

An important concomitant effect of statins is that they reduce the risk for cardiovascular events. As statins have been shown to reduce atherosclerotic stenoses progression of the coronary and the peripheral arteries, their effects may be expected to be generalized and to affect the aorta, main renal arteries and their segmental branches. [25] Although renal function progression and reaching end-stage renal failure are major outcomes in ARAS patients, mortality is essentially cardiovascular in origin. ARAS is strongly associated with other cardiovascular comorbidity. Furthermore, this risk is emphasised by the fact that impaired renal function is an independent predictor of cardiovascular morbidity. Therefore, a reduction of overall cardiovascular risk factors is essential for the prognosis of ARAS patients. This also includes the cessation of smoking, which in addition to being a risk factor for cardiovascular disease also has adverse renal effects. [26]

In conclusion, observational studies have yielded evidence that stent placement in azotemic ARAS patients can preserve renal function. Medical therapy aimed at lowering lipids (statins) and controlling hypertension also seems promising in reducing renal failure and furthermore, could have a favourable impact on the increased cardiovascular risk of these patients. In this trial, we will investigate whether stent placement in patient with ARAS and renal failure offers an extra benefit for the prevention of renal dysfunction progression compared to optimal medical treatment alone.

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Chapter 7

Efficacy and safety of stent placement in patients with impaired renal function and atherosclerotic renal artery stenosis: the STAR study

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Submitted

Summary

Background

Atherosclerotic renal artery stenosis (ARAS) is associated with progressive loss of renal function. Observational studies suggest this progressive loss can be prevented by renal artery stenting. There is however no evidence supporting a beneficial effect of stent placement, while it may potentially have serious complications.

Methods

We randomly assigned 140 patients with a creatinine clearance <80 mL/min/1.73 m^2 and an ARAS ≥50% to medical treatment only (medication group, 76 patients) or medical treatment plus stent placement (stent group, 64 patients). Medical treatment consisted of antihypertensive agents, a statin and aspirin. The follow-up was 2 years. The primary end point was a ≥20% decrease in creatinine clearance from baseline. Secondary end points included safety and cardiovascular morbidity and mortality. Analyses were performed on intention-to-treat basis.

Findings

In the stent group, 46 patients underwent stent placement. No stent was placed in eighteen for various reasons. In this group 10 patients (16%) reached the primary end point versus 16 patients (22%) in the medication group (hazard ratio 0.73 with 95% confidence interval 0.33-1.61). The stent group, however, demonstrated serious complications including two procedure-related deaths (3%), one late death secondary to an infected hematoma and one patient developing renal failure secondary to cholesterol embolism. The other secondary end points were equally distributed between the groups.

Interpretation

Stent placement in addition to medical treatment does not seem to delay progression of impaired renal function but exposes to procedure-related complications. Our findings favour a conservative therapeutic approach to patients with ARAS, focused on cardiovascular risk factor management.

Introduction

Current guidelines on treatment of atherosclerotic renal artery stenosis (ARAS) to preserve renal function state that revascularisation with stent placement is a reasonable indication for patients with bilateral disease or a solitary functioning kidney, whereas it may be considered for patients with a unilateral stenosis. [1] Evidence for the clinical benefit of endovascular treatment is scarce and not supported by controlled studies. [2,3]

The natural history of ARAS has been characterized by progression with consequent loss of renal function. [4-6] ARAS patients are considered high risk patients as their absolute cardiovascular risk exceeds that of need for renal replacement therapy. [7] Impaired renal function in these patients is assumed to be caused not only by reduced blood flow to the kidney, but also by loss of microvascular renal perfusion and by renal fibrosis. [8] These conditions are driven by hypertension, hyperlipidemia, diabetes mellitus, and smoking. Until present, intervention studies have mainly focused on relieving the stenosis, showing stabilisation or improvement of renal function in the majority of patients. [3] No studies have addressed the role of aggressive medical therapy affecting the intra-renal component of the disease.

The number of percutaneous renal artery interventions is increasing rapidly. [9,10] While there are no controlled trials supporting this strategy, it has been reported that stenting may be complicated by serious morbidity and even mortality. [2,3,11,12] We therefore undertook the first randomized trial assessing the efficacy and safety of stent placement compared to medical treatment alone in patients with renal impairment and ARAS.

Methods

Study design

This trial was a multicenter randomized trial in 10 centers involving 140 patients. Patients were randomly assigned to receive medical treatment only or medical treatment combined with renal artery stent placement. The patients were monitored for two years. The study protocol was approved by the local institutional review board at each participating site. Written informed consent was obtained from each participating patient.

Patients

Criteria for eligibility were impaired renal function, ostial ARAS, and stable blood pressure. Impaired renal function was defined as an estimated creatinine clearance <80 mL/min/1.73 m^2 according to the Cockcroft and Gault formula. The mean of two fasting serum creatinine values determined within one month was used to assess renal function. Ostial ARAS was defined as a luminal reduction of ≥50% of the renal artery within 1 cm of the aortic wall, in the presence of atherosclerotic changes in the aorta. Stenosis evaluation could be performed on computed tomographic angiography (CTA), magnetic resonance angiography (MRA), or angiography (digital subtraction angiography). All angiograms were evaluated by two

experienced radiologists. Finally, the patients were required to have stable blood pressure control, if possible in the absence of angiotensin converting enzyme (ACE) inhibitors or angiotensin-II receptor antagonists.

Exclusion criteria comprised a renal size <8 cm, renal artery diameter <4 mm, an estimated creatinine clearance < 15 mL/min/1.73 m^2, diabetes mellitus with proteinuria (>3 g/24 hr), and malignant hypertension. Details on the protocol have been described elsewhere. [13]

Randomisation

Randomisation was stratified per center and for unilateral or bilateral stenosis. A unilateral stenosis was defined as unilateral ostial stenosis with either a truncal stenosis or no stenosis in the contra-lateral artery. A bilateral ostial stenosis was defined as ostial stenosis on both sides, unilateral ostial stenosis with contra-lateral occlusion or solitary kidney with ostial stenosis.

Medication group

Hypertension was treated with diuretics, calcium antagonists, beta-blockers and alpha-blockers. ACE-inhibitors and angiotensin-II receptor antagonists together with increasing doses of diuretics could be used only when other classes of anti-hypertensive agents had failed. The target blood pressure was < 140/90 mmHg. Irrespective of the serum cholesterol levels, the patients were treated with 10 mg of atorvastatin and if this was well tolerated the dose was raised to 20 mg. [13] In the original study protocol cerivastatin was the prescribed statin. This drug was however withdrawn from the market and therefore replaced by atorvastatin. All patients received anti-platelet therapy, aspirin 75-100 mg/OD. Smokers were advised to stop. Indications for angiography and subsequent treatment when necessary during follow-up were therapy refractory hypertension (blood pressure > 180/100 mmHg and mean blood pressure > 160/95 mmHg on 24 hour ambulant monitoring while on maximum dose of all classes of antihypertensive agents), malignant hypertension, and pulmonary edema. [13]

Medication plus stent group (Stent group)

Medical treatment in this group was the same as in the medication group. A Palmaz-Corinthian IQ/Palmaz-Genesis stent (Johnson & Johnson Medical, NV/SA) was placed in every ostial stenosis, according to a standardized protocol. [14] During this session, truncal stenoses were treated by balloon angioplasty. Technical success was defined as a residual stenosis <50%. Patients allocated to be stented started with aspirin 75-100 mg/OD the day before admission. During follow-up, re-intervention was allowed to achieve patent renal arteries when a re-stenosis was suspected based on a ≥20% decrease in renal function or on clinical grounds as described before. Ostial stenoses were treated by stent placement, truncal and in-stent stenoses by balloon angioplasty.

Follow-up

Patients were followed-up at 1, 3 and subsequently every 3 months after start of treatment for a period of 2 years. Fasting serum creatinine was recorded at every visit, as well as blood pressure three times in sitting position. Total cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, and triglycerides were recorded after 1, 3 and 6 months, then every 6 months. All centers were monitored yearly for quality control of the data.

End points

The primary end point was a ≥20% decrease in estimated creatinine clearance compared to baseline, based on two repeated measurements. In the medication group, this was the definitive end point. In the stent group, at this point a diagnostic test was done to rule out re-stenosis of the renal artery. When there was no re-stenosis the end point was reached. In case of a re-stenosis, a re-intervention was performed and the primary end point was reached only if the ≥20% reduction in creatinine clearance persisted one month after re-intervention.

Both groups of patients were also compared in terms of secondary end points comprising complications, effect on hypertension, incidence of therapy refractory, malignant hypertension, and pulmonary oedema, cardiovascular morbidity and mortality, and total mortality. Peri-procedural complications were defined as occurring within 30 days after start of treatment. The end points of cardiovascular morbidity and mortality were independently evaluated by the clinical event committee according to a pre-existing protocol. [15]

Statistical analysis

The sample-size calculation was based on an expected reduction in the incidence of progressive renal failure from 50% in the medication group to 30% in the stent group, with a power of 90%. [16] To detect this difference at a significance level of 5%, we needed to recruit 140 patients. [13] Analysis took place according to the intention-to-treat principle. Outcome measures in both treatment arms were compared for all patients at the time of reaching the primary end point or at 2 years. The cumulative incidence of primary end points was illustrated by an estimated survival curve (Kaplan Meier, 1 minus survival) and compared across groups using the log-rank test. Crude hazard ratios (with 95% confidence intervals [CI]) comparing the stent group with the medication group (reference) for each end point were obtained from Cox proportional hazards regression models. To assess the modifying effect of the type of stenosis, the statistical significance of the product term of type of stenosis and randomisation was determined. For patient characteristics, differences between groups were tested with chi-squared test for discrete variables, student's t-test for continuous variables with normal distribution, and Wilcoxon rank-sum test for variables not normally distributed. A two-sided P-value <0.05 was considered to indicate statistical significance.

Table 1. Baseline characteristics of the study participants*

	Medication group n = 76	Stent group n = 64
Age (yr)	67 ± 9	66 ± 8
Male sex no. (%)	45 (59)	43 (67)
Vascular history no. (%)	59 (78)	54 (84)
Diabetes mellitus	18 (31)	16 (30)
Cerebrovascular disease	18 (31)	15 (28)
Heart failure	7 (12)	5 (9)
Aneurysm abdominal aorta	9 (15)	7 (13)
Peripheral artery disease	30 (51)	26 (48)
Coronary artery disease	32 (54)	23 (43)
Current or past smoking no. (%)	52 (68)	46 (72)
Current smoking no. (%)	15 (20)	20 (31)
Renal function		
Serum creatinine (μmol/L)	145 ± 51	154 ± 60
Estimated creatinine clearance (mL/min/1.73 m^2)	46 ± 16	45 ± 15
Blood pressure		
History of hypertension no. (%)	73 (96)	63 (98)
Systolic blood pressure (mmHg)	163 ± 26	160 ± 25
Diastolic blood pressure (mmHg)	82 ± 12	83 ± 13
Antihypertensive drugs		
No. of drug categories	2.9 ± 1.0	2.8 ± 1.0
Regimen no. (%)		
ACE-inhibitors	23 (30)	21 (33)
Angiotensin-II receptor antagonists	18 (24)	17 (27)

Table 1. Continued

	Medication group n = 76	Stent group n = 64
Laboratory data		
Cholesterol (mmol/l)	5.1 ± 1.0	4.9 ± 1.2
HDL-cholesterol (mmol/l)	1.2 ± 0.4	1.2 ± 0.4
LDL-cholesterol (mmol/l)	3.1 ± 0.9	2.8 ± 1.3
Triglycerides (mmol/l)	1.8 ± 1.2	2.2 ± 1.6
Glucose (mmol/l)	6.2 ± 2.0	5.9 ± 1.6
Proteinuria (g/24h) †	0.14 (0.08-0.36)	0.19 (0.1-0.5)
Prior renal artery intervention no. (%)	8 (11)	7 (11)
Balloon angioplasty	7 (9)	6 (9)
Stent	1 (1)	1 (2)
Evaluation of the stenosis no. (%)		
CTA	24 (32)	23 (36)
MRA	39 (51)	35 (55)
Angiography	13 (17)	6 (9)
Type of ostial stenosis no. (%)		
Unilateral	41 (54)	32 (50)
Bilateral	35 (46)	32 (50)
Occlusion/shrunken kidney no.	11	14
Single kidney no.	3	1
Degree of stenosis most affected kidney no. (%)		
50 - 70%	24 (32)	22 (34)
70 - 90%	35 (46)	20 (31)
> 90%	17 (22)	22 (34)

* Plus-minus values are means ±SD.
† Median with inter-quartile range in parenthesis.

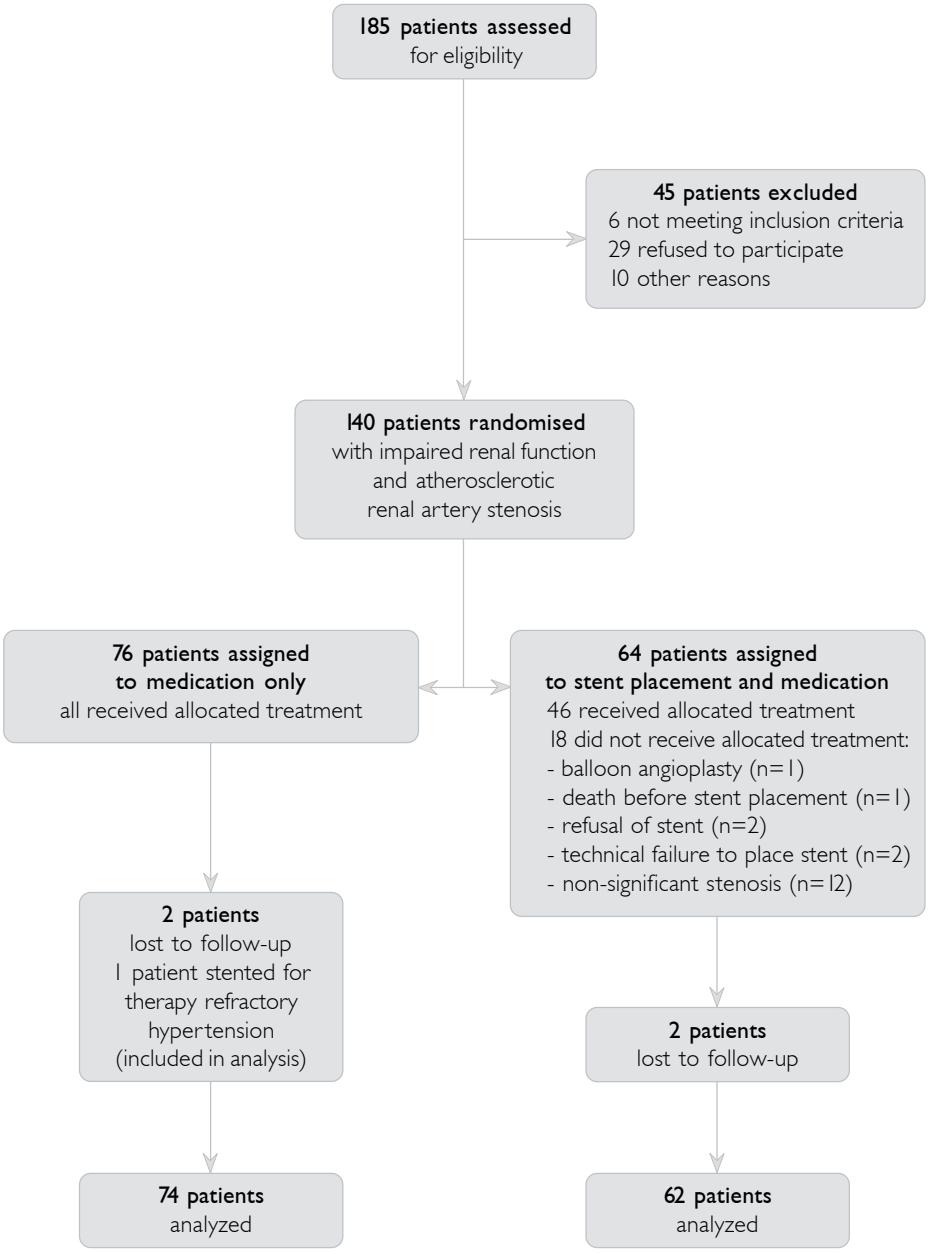

Figure 1. Trial profile.

The trial was monitored by an independent data and safety monitoring board. A planned interim analysis was performed after 70 patients had been included and followed for 2 years.

Results

Study patients

Between June 2000 and December 2005, 140 patients were randomly assigned to medical treatment only (n = 76) or medical treatment with additional stent placement (n = 64) and followed for 2 years. The difference in numbers of patients per group can be explained by the stratification by center and by type of stenosis (Table 1). Three patients in the stent group did not receive the assigned treatment after randomisation: one patient died before stent placement and 2 patients declined stent placement.
In the stent group, a stent was placed in 46 patients, with a residual stenosis of less than 20% in all patients. In one patient the stenosis was truncal and treated with balloon angioplasty. No intervention was performed in 14 patients. This was due to an ARAS <50% at the time of intended stent placement in 12 patients (19%), an artery of too small calibre in one and failure of stent placement because the guide wire could not pass the >95% stenosis in the last one (Figure 1). All patients were followed-up in the assigned arm in accordance with the intention-to-treat principle.

Primary end point

Sixteen patients (22%) in the medication group reached the primary end point versus 10 (16%) in the stent group (two of whom were not stented at the beginning of the trial). The hazard ratio (HR) of the stent versus medication group for reaching the primary end point was 0.73 (95% CI 0.33-1.61, Table 2). In both groups the primary end point was reached after a mean follow-up of 10 months (SD 7). In the stent group, before reaching the end point, 5 of the 10 patients had a re-angiography showing no stenosis in three and a re-stenosis in two (one treated by stent, the other by balloon angioplasty). In all of these patients the >20% decrease in creatinine clearance persisted one month after re-angiography. In 5 patients no angiography was done. This was due to concurrent end-stage malignancy in two patients and reaching end-stage renal disease before re-intervention in another two. In the last patient, a renogram demonstrated normal kidney perfusion suggesting a patent stent, therefore no angiography was done.

The event-free survival by treatment arms is illustrated using Kaplan Meier curves (Figure 2, P = 0.43). The type of stenosis (unilateral or bilateral) was not a statistically significant effect modifier (P = 0.41).

Table 2. Primary and secondary end points until the primary end point is reached or 2 years follow-up

	Medication group n = 76	Stent group n = 64	Crude HR † (95% CI)
Lost to follow-up in the first 2 years	2	2	
	n= 74	n= 62	
Primary end point ‡ no. (%)	16 (22)	10 (16)	0.73 (0.33-1.61)
Unilateral stenosis §	8 (11)	3 (5)	0.48 (0.13-1.81)
Bilateral stenosis §	8 (11)	7 (11)	0.95 (0.34-2.61)
Secondary end points no. (%)			
Therapy refractory hypertension	3 (4)	0	-
Malignant hypertension	0	0	-
Pulmonary oedema	1 (1)	0	-
Cardiovascular morbidity			
Heart failure	3 (4)	1 (2)	0.39 (0.04-3.71)
Coronary artery disease	3 (4)	3 (5)	1.16 (0.23-5.73)
Peripheral artery disease	7 (9)	4 (6)	0.67 (0.20-2.28)
Cerebrovascular disease	1 (1)	0	-
AAA	0	0	-
Mortality of all cause	6 (8)	5 (8)	0.99 (0.30-3.24)
Cardiovascular mortality	4 (5)	2 (3)	0.59 (0.11-3.25)
Procedure related mortality	0	2 (3)	-

* Chi-squared test for discrete variables and t-tests for continuous variables.
† HR: hazard ratio with the medication group used as reference group.
‡ Primary end point: ≥20% decrease in estimated creatinine clearance compared to baseline. In the stent group, the primary end point was reached if the ≥20% reduction in creatinine clearance persisted 1 month after re-intervention.
§ Subgroup analysis for patients with either unilateral stenosis or bilateral stenosis.

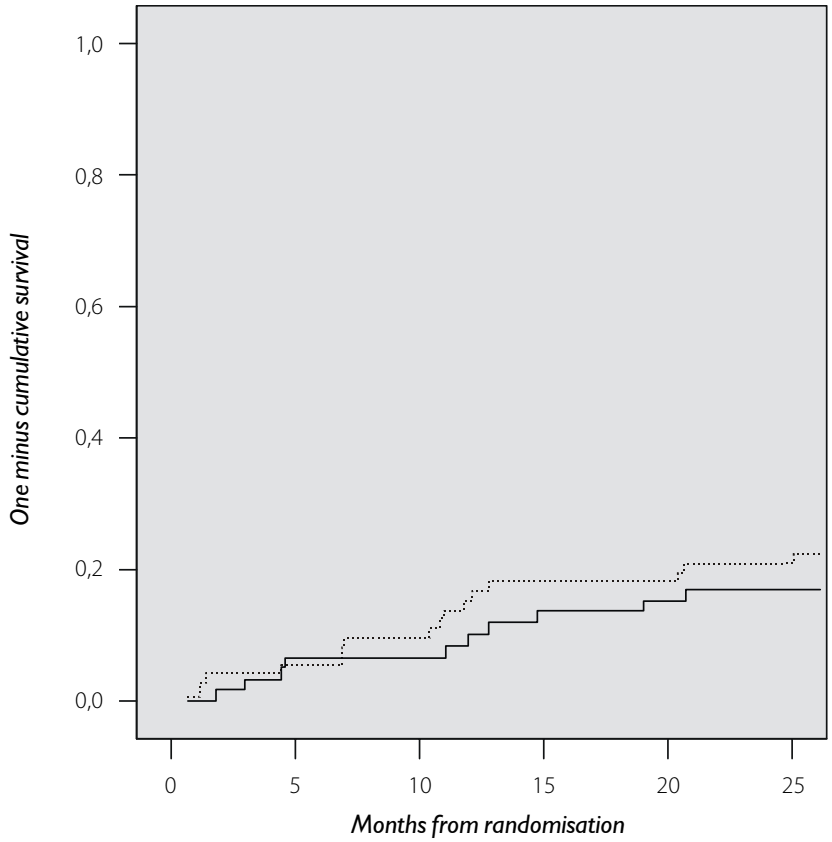

Figure 2. Survival curves for the primary end point comparing the medication group (dotted line) with the stent group (continuous line) during 2 years of follow-up.

Secondary end points

There were no statistically significant differences between the groups in terms of blood pressure control and occurrence of cardiovascular morbidity and mortality (Table 2). Procedure related deaths occurred only in the stent group. Three patients in the medication group developed therapy refractory hypertension. In one patient no intervention was done because of a kidney <8 cm. In the second, there was a technical failure to place a stent. In the third patient a stent was placed successfully. One patient in the medication group had pulmonary oedema. This occurred in combination with a 20% decrease in creatinine clearance.

Complications

Two patients in the stent group died within 30 days following the stent placement. Both deaths were procedure-related. In the first patient embolisation after perforation of the renal artery was required. The patient died of an ischemic stroke three days later. The second patient had a perforation of a renal artery branch. The artery was embolised but despite re-intervention the patient went into hypovolemic shock and died.
The most common complications after stent placement were minor and mainly consisted of a hematoma at the puncture site (11 patients, 17%). In one of these patients, secondary infection in the groin required surgical reconstruction. The patient thereafter developed end stage renal failure, pulmonary oedema, and heart failure and died 6 months after the procedure. In two patients the procedure was complicated with a false aneurysm of the femoral artery. Injury to the kidney or renal artery occurred in five patients. This was never associated with loss of renal function and additional intervention was never required. Minor side effects of medication were reported in 15 patients in the medication group versus 4 in the stent group.

After re-angiography in the stent group, permanent dialysis was needed in one patient after cholesterol embolism. In another patient, the re-angiography was complicated by a groin hematoma.

Patient characteristics

The patient characteristics at the time of reaching the primary end point or 2 years follow-up are summarized in Table 3**.** There were no differences between the groups in terms of renal function and blood pressure. Although both groups showed improvement of blood pressure during the trial, this was obtained with equal numbers of antihypertensive drugs. The patients in the medication group had higher cholesterol and LDL-cholesterol levels, despite a slightly higher dosage of statin.

Discussion

Our results show that in patients with impaired renal function and ARAS there is no difference in progression of renal failure between patients treated with medication only and patients treated with stent and medication after 2 years. There was however a considerable number of stent-related complications including two procedure related deaths, one death secondary to an infected hematoma and one deterioration of renal function resulting in dialysis.

Revascularisation of the renal artery to preserve renal function is based on the assumption that ischemia contributes to renal insufficiency, and that correction of the stenosis and restoration of renal perfusion will stabilize or improve renal function. The ultimate goal is to prevent or delay the need for renal replacement therapy. This is the first controlled trial assessing whether revascularisation can indeed preserve renal function. Our data show

Table 3. Patient characteristics at the time the primary end point is reached or 2 years follow-up*

	Medication group n = 76	Stent group n = 64	*P* †
Lost to follow-up + mortality in the first 2 years	8	7	
	n = 68	n = 57	
Renal function			
Serum creatinine (µmol/l)	168 ± 76	156 ± 69	0.37
Estimated creatinine clearance (mL/min)	46 ± 19	50 ± 22	0.29
Blood pressure ‡			
Systolic blood pressure (mmHg)	155 ± 26	151 ± 23	0.40
Diastolic blood pressure (mmHg)	79 ± 11	77 ± 12	0.44
Blood pressure on target § no. (%)	20 (29)	18 (32)	0.95
Medication use no. (%)			
No. of antihypertensive drug categories	2.9 ± 1.1	2.6 ± 1.4	0.30
ACE-inhibitors	21 (31)	21 (37)	0.48
Angiotensin-II receptor antagonists	24 (35)	14 (25)	0.19
Atorvastatin or other statin	63 (93)	48 (84)	0.14
Mean dose atorvastatin (mg)	23 ± 13	19 ± 9	0.08
On lipid-lowering drug	63 (93)	51 (89)	0.53
Anti-platelet or anticoagulant therapy	58 (85)	48 (84)	0.87
Laboratory data			
Cholesterol (mmol/l)	4.4 ± 1.0	4.0 ± 0.9	0.01
HDL-cholesterol (mmol/l)	1.2 ± 0.4	1.1 ± 0.3	0.19
LDL-cholesterol (mmol/l)	2.5 ± 0.8	2.0 ± 0.6	0.003
Triglycerides (mmol/l)	1.9 ± 1.1	2.0 ± 1.0	0.51
Proteinuria (g/24h) ¶	0.15 (0.09-0.6)	0.16 (0.1-0.3)	0.92
Current smoking no. (%)	18 (27)	15 (26)	0.99

* Plus-minus values are means ± standard deviation.

† Chi-squared test for discrete variables and t-tests for continuous variables.

‡ Target blood pressure was defined as <140/90 mmHg.

§ The systolic and diastolic blood pressure improved in both groups compared to baseline, with the same number of antihypertensive drugs. The mean difference in systolic blood pressure was -9.0 mmHg (p = 0.013) in the medication group and -9.5 mmHg (p = 0.021) in the stent group. The mean differences in diastolic blood pressure were -3.9 mmHg (p = 0.011) and -6.9 mmHg (p = 0.001) for the medication and stent groups respectively.

¶ Median with inter-quartile range in parenthesis.

a small numerical effect on the primary end point of stent placement compared to medication only (16% versus 21%). However, this difference did not reach significance, while risk factors for atherosclerosis were also numerically slightly higher in the medication group. The fact that progressive loss of renal function may occur despite successful revascularisation underscores the complex aetiology of ischemic nephropathy with an important intra-renal (parenchymal) component strongly affected by risk factors for atherosclerosis.

We found that renal artery intervention was complicated by procedure-related death in 2 patients (3%). Previous intervention studies among ARAS patients treated specifically for renal failure have shown a 0-10% 30-day all cause mortality. [16-23] Considering the studies with a prospective design, the procedure-related mortality was found in 0-3.6% and need for dialysis within 30 days after stent placement in 0-4% of the patients. [16, 17,20] These rates are in accordance with our results. All our interventional radiologists had an extensive experience in renal stenting of more than ten years and eight of the ten participated in large scale studies in patients with renovascular disease. [24-26]

An important finding of our study was a lower primary event rate as anticipated. Explanation for this must be the improved cardiovascular risk management in recent years achieved with the introduction of lipid-lowering drugs that was used in both groups of patients. The use of statins has shown a beneficial effect of lipid-lowering with reduction of proteinuria in patients with chronic kidney disease and reduction in kidney function loss in patients with cardiovascular disease.[27,28] Apparently it has delayed the progression of loss of renal function considerably. Unfortunately, this has a negative effect on our study design. The low primary event rate reduces the power of the trial. At the time we designed our trial, ten years ago, few studies were available on the natural course of renal function in ARAS patients, and those who were, were mainly done in patients with renovascular hypertension with generally better renal function. Schreiber et al. demonstrated that 38% of the patients had a 20% deterioration of renal function after a mean of 52 months, whereas Dean et al. showed progressive renal failure in 46% after 44 months. [4,29] The only study, at the time, in patients with impaired renal function specifically, was by Beutler et al. showing that 55% of the patients had decreasing renal function (>20%) in the year prior to intervention. [16] In our power calculation, we therefore considered an event rate of 50% in two years for the medication group. An important consequence of this lower event rate is moreover, that to reach a clinically worthwhile superiority of the stent, an extremely large population will need to be studied, while only a small proportion of patients would really benefit from the stent. And this would still be at the price of serious complications and high costs. These aspects reinforce our conclusion our study demonstrates that the balance between the potential advantage in terms of renal function and disadvantage in terms of potential complications is not in favour of stent placement.

Although it did not reach statistical significance, patients with a unilateral stenosis were more likely to benefit from stent placement than patients with bilateral disease. This could indicate a trend that early treatment is more beneficial. Further follow-up will have to confirm this finding. In terms of blood pressure, prior studies comparing balloon angioplasty of the renal artery and medical therapy in patients with renovascular hypertension suggested a small beneficial effect in the intervention group. [24,26] In our ARAS patients with renal dysfunction, improvement of blood pressure compared to baseline was obtained in both groups. However, the systolic and diastolic blood pressures were not different across the groups, with equal numbers of antihypertensive drugs.

A limitation of this study is that we had a considerable number of patients with a non-significant stenosis at inclusion. By allowing randomisation on results of non-invasive diagnostic tests, we accepted the occurrence of these non-significant stenoses as false positives as the specificity of CTA is 92% and 84% for MRA for the diagnosis of ARAS. [30] However, these must have occurred in both treatment arms. This was at least partially compensated, as we included 10% extra patients for eventual drop-outs, which in fact was only 3%.

In conclusion, this is the first trial comparing medication only to stent placement in addition to medication in patients with impaired renal function and ARAS with 2 years of follow-up. Our findings favour a conservative therapeutic approach to patients with ARAS, focused on cardiovascular risk factor management.

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Chapter 8

General discussion

Cross-talk between the kidney and the cardiovascular system

Impaired renal function, either mildly or severely, is a common finding. In a population based series, approximately 18% of the subjects had decreased renal function. [1] The national kidney foundation defines chronic kidney disease (CKD) as persistent kidney damage, as reflected by a glomerular filtration rate of less than 60 mL/min per 1.73 m^2 of body surface area for more than three months. [2] Chronic kidney disease is a serious public health problem as approximately 1 out of 20 patients will eventually progress to end-stage renal failure or renal replacement therapy. [3]

Evidence for the relationship between renal dysfunction and cardiovascular events was first recognized in the dialysis population in which the incidence of cardiovascular death is strikingly high. Approximately 50% of the individuals with end-stage renal disease (ESRD) die from a cardiovascular cause, which is 15 to 30 times higher than in the age-adjusted general population. [4] However, the impact of renal insufficiency on the development of atherosclerotic cardiovascular disease probably may already begin with minor renal dysfunction. [5]

Impaired renal function was shown to be an independent and strong predictor of cardiovascular disease (CVD) in subgroups of patients with hypertension, heart failure and myocardial infarction, but also in the general population. [1, 6-8] In this thesis we demonstrated that there is indeed a strong relationship between renal failure and CVD, even in patients with known manifest vascular disease. While renal function and renal size decrease faster with age in patients with more severe atherosclerosis (***chapter 2***), the patients with impaired renal function are more likely to develop CVD, independently of other risk factors such as hypertension and diabetes mellitus (***chapter 3***).

One of the mechanisms that seems to be central in the genesis of many different aspects of cardiovascular disease in renal patients, is endothelial dysfunction. Impairment of endothelial function is recognised as one of the initial mechanisms that lead to atherosclerosis. [9] Experimental evidence suggests that microvascular endothelial dysfunction participates in the mechanism that leads to progression of renal disease, which in turn may exacerbate endothelial dysfunction and contributes to acceleration of atherogenesis. Endothelial dysfunction and remodelling of blood vessels may participate not only in the vascular complications in patients with kidney disease, but also in the maintenance of elevated blood pressure. [10] Nitric oxide is an important regulator of vascular tone and tissue perfusion. Reduced bioavailability of nitric oxide appears to be one of the main factors involved in chronic renal failure-associated endothelial dysfunction, because of increased oxidative stress in the vascular wall. [10] Oxidative stress is caused by an imbalance between the production of reactive oxygen and the ability of the biological system to readily detoxify the reactive intermediates or easily repair the resulting damage. This, in turn, may contribute to the increase in circulating inflammatory biomarkers in CKD. In this line of thought, impaired vascular endothelial function may be linked with vascular leakage of albumin, resulting in albuminuria: the leaky renal vessel as a reflection of the permeability of the vasculature in general. [11]

Atherosclerotic vascular disease: to stent or not to stent?

A specific aspect of the relationship between renal function and CVD is atherosclerotic renal artery stenosis (ARAS), as we expect causality between the stenosis and loss of renal function on the one hand, and increased risk for future CVD in a patient with manifest vascular disease (i.e. ARAS) on the other hand.

Impaired renal function in ARAS patients is a complex entity as is illustrated by the figure. As far as the symptoms are concerned, a strong association exists between renal function and hypertension. Considering ARAS, it is an obstruction in the blood flow to the kidney but also an expression of atherosclerosis, a generalised entity affecting both arteries of smaller and larger calibre. Renal artery intervention by balloon dilatation and stent placement has emerged as an effective way to treat the stenosis and keep the artery patent (***chapter 5***). But much uncertainty has arisen as far as the benefit of stent placement compared to conservative treatment is concerned, especially since a minority of the patients demonstrated improvement of renal function after renal artery intervention. Conversely, procedure-related complications such as worsening of renal function, dissection, cholesterol emboli, contrast nephropathy, hematoma, but also death, need to be considered. In the STAR trial we assessed the benefit of stent placement in a randomised fashion, comparing medical treatment to medical treatment plus stent placement in patients with impaired renal function and a >50% stenosis of the renal artery due to atherosclerosis (***chapter 6***). We found no difference in progression of renal failure between patients treated with medication only and patients treated with stent and medication after 2 years (***chapter 7***). Several aspects became apparent from this study.

First, the number of events, defined as a >20% decrease in renal function, was lower than anticipated in both groups. When designing the study, ten years ago, available literature stated that about 50% of the patients treated conservatively would develop progressive loss of renal function. [12-14] In practice only 21% of the patients did. This is in fact an important finding, as it seems to reflect the improved cardiovascular risk management achieved in recent years. Introduction of lipid-lowering drugs has allowed better control of renal function. [15, 16]

Second, serious complications occurred following stent placement, with a mortality rate of 3%. This number seems higher than in previous reports about stenting, but these studies were mostly performed in patients with renovascular hypertension and not impaired renal function specifically. [17] In fact, the few studies assessing the effect of stent placement for renal failure report similar mortality rates. [18-22] However, these rates seem to have been taken for granted, as authors believed the observed benefit of stent placement was clinically worthwhile. These studies had no conservatively treated controls to weigh that benefit.

And third, there were less primary end points in the stent group compared to the medication group, but the difference was not statistically significant. Considering the fact that the >20% decrease in renal function is a surrogate end point of ESRD, which we want to

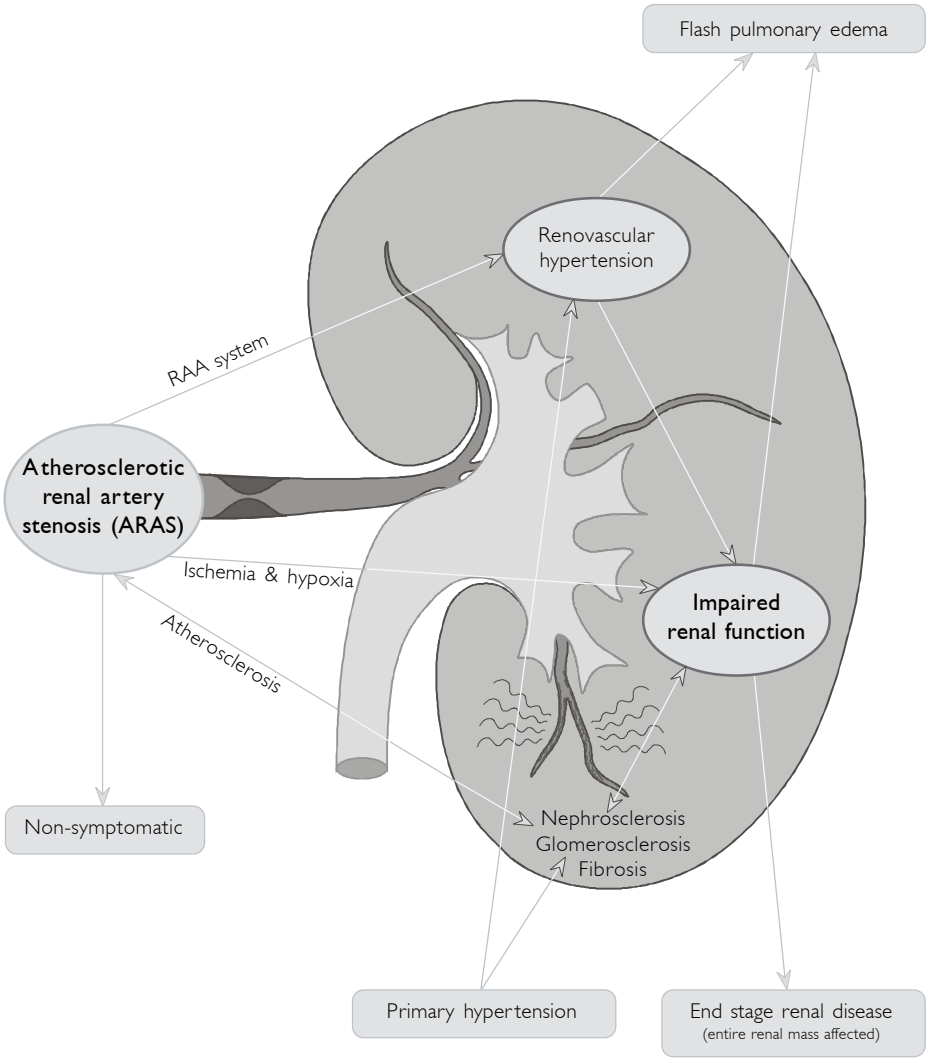

Figure. Simplified illustration of the aspects involved in renovascular disease, with respect to renal function implications in particular. RAA system: renin-angiotensin-aldosterone system; ACE-inhibitor: angiotensin-converting enzyme inhibitor; ARB: angiotensin-II receptor blocker.

prevent, the advantage of stent placement is not clinically significant either. The low primary event rate achieved by medication only makes it difficult for the stent to surpass that benefit.

Endovascular renal artery therapy has gained ground as it offered less initial risk compared to reconstructive surgery, essentially in older and high risk patients. Although the long term patency still needed to be established, in uncontrolled studies the clinical benefit seemed promising. [12, 18] Stent placement now has to compete with medical therapy, which has greatly improved over the years and is non-invasive. These older patients, with more diffuse atherosclerosis, may have a greater risk of complications and may not live long enough to reap the benefits of renal artery interventions. Overall, the balance between the costs and benefits is not in favour of stent placement. An ARAS patient might be considered just another patient with manifest cardiovascular disease, needing good risk factor modelling.

Considerations and future perspectives

Screening for high risk patients and risk factor modification

Numerous scoring tools have been developed to stratify the risk of patients for the occurrence of CVD. The Framingham algorithm and the SCORE (systematic coronary risk evaluation) risk chart are currently widely used in the USA and in Europe, respectively. [23, 24] The factors considered in these risk estimation systems usually include (systolic) blood pressure, glucose levels, lipid levels (cholesterol), smoking habits, age and gender. These do not include renal function. Assessment of renal function is easy, widely available and cheap, and the estimated creatinine clearance (GFR) can be calculated easily using the Cockcroft and Gault formula or the Modification of Diet in Renal Disease (MDRD) equation. [25] With the accumulating evidence that renal function is a strong and independent predictor of future CVD in high as well as low risk patients, renal function deserves a spot in the risk algorithms, to detect patients at increased risk for CVD.

Although the prevention of end-stage renal disease remains a very important goal in patients with kidney disease, more effective interventions are clearly needed to reduce the cardiovascular burden in this population. [26] However, studies have shown "therapeutic nihilism" for patients with impaired renal function, with simultaneous worsening of renal function. Among patients with end-stage renal disease, less than 50% are taking a combination of aspirin, beta-blockers, angiotensin-converting-enzyme inhibitors, and statins. [27] Potential reasons include the concern about worsening renal function and therapy-related toxic effects related to reduced clearance. [2,28-30] However, studies show that, when appropriately monitored, cardiovascular medication and interventional strategies can safely be administered to those with renal impairment and yield similar benefits. [31,32]

ASTRAL & CORAL

The STAR trial is the first randomised trial in renal artery stenosis and impaired renal function comparing stent placement to medical treatment. However, there are other ongoing trials with similar research questions. The ASTRAL (Angioplasty and STent for Renal Artery Lesions) trial included ARAS patients when there was substantial uncertainty whether to offer revascularisation in addition to medical treatment. [33] There were no criteria concerning blood pressure or renal function levels. The primary end point was defined as a difference in mean rates of progression of renal function. ASTRAL included 750 patients and it appears that they come to the same conclusions as we did in STAR (personal communication), finding no benefit for the stent compared to medication only. The emphasis of the large scale CORAL trial (Cardiovascular Outcomes in Renal Atherosclerotic Lesions) is more on the long term cardiovascular outcomes than on renal function. [34] The feasibility of the CORAL trial might be jeopardized by the findings of STAR and ASTRAL, as it will be ethically difficult to randomise patients to either stent or medication, knowing that two trials found no superiority of stenting, and exposing patients to potentially serious complications.

Unilateral ARAS

The randomisation of the STAR trial was stratified by unilateral and bilateral disease. Intuitively, the most affected patients, with bilateral stenosis, would be the ones to profit the most from an intervention. However, our findings suggest the opposite. Stent placement tends to prevent progression of renal failure in patients with unilateral instead of bilateral ARAS. Patients with unilateral ARAS generally have a better renal function. The importance of ARAS is often mirrored by its hemodynamical significance. However, the generalised process of atherosclerosis develops gradually, affecting both smaller and larger arteries, and eventually obliterates the lumen of the renal artery. [35,36] The renal parenchyma is therefore also affected gradually. This could mean that precisely in the early stages of atherosclerosis, when stenoses are less severe or unilateral, treatment of the stenosis might result in functional benefit. Damage to the kidney might still be reversible at this stage. However, a relationship between the degree of stenosis and renal function has not been found. [37] Cardiologists are increasingly performing "drive-by" renal arteriographies to identify ARAS in as early a stage as possible, considering ARAS as a risk factor for premature cardiovascular events. [38] Patients with low grade ARAS and unilateral disease might constitute a subgroup of patients where stent placement would be indicated. In the STAR study, a planned extended follow-up of 5 years is currently ongoing. The longer follow-up of these patients might confirm this hypothesis.

Distal protection device

A new development in stent placements is the use of a distal protection device. These have been introduced to capture atheromatous emboli scattered during endovascular interventions, as these might cause acute decline of renal function due to the procedure, and thereby abolish the beneficial effect of stenting. [19] This device consists of a polyurethane filter and a nitinol framed 'basket' at the distal end of a guidewire. The distal protection device has been used in coronary and carotid circulation with variable success. The value of such a protection device is still under investigation for the renal arteries (RESIST trial, clinical trials.gov registration number NCT00234585). Difficulties that are encountered comprise anatomical aspects with a small arterial calibre and early branching of the artery. Whether the atheromatous emboli have a clinical significance or whether they occur without consequence is uncertain. We did not observe acute deterioration of renal function following stent placement procedures in the STAR trial. It would rather be a coincidence if the loss of renal function caused by the embolic debris would exactly equal the renal function gained by the intervention, and making us detect neither benefit nor disadvantage from stent placement. This suggests that the effect of atheromatous emboli scattered in the kidney is rather small.

Improvement of diagnostic tools

As observed in the STAR study, the diagnosis of ARAS is not straight forward. Non-invasive imaging tools using computed tomography (CT) or magnetic resonance imaging (MRI) are promising, but have limited specificity. [39] New and faster imaging techniques and sequences develop at a quicker rate than patient-related research can be performed. Multirow detector computed tomography (MDCT) has demonstrated superior accuracy in the assessment of renal anatomy. [40] Whether this applies to ARAS detection remains to be studied. In MRI, new sequences using blood oxygen level dependent (BOLD) magnetic resonance measure the metabolic activity and oxygen consumption in the kidney. [41] This might help to identify patients with still reversible parenchymal damage. In our efforts to measure renal blood flow in the renal arteries with MRI (***chapter 4***) we expected to develop a method to characterise the blood flow profile and thereby obtain information on health of the kidneys (intra-renal resistance and reactivity). Unfortunately, the variability of the measurements was too large to be reliable. Measurement of the resistive index of the kidney by ultrasound has been proposed as well, as a tool to select patients prone to respond positively to revascularization. [42] So far, these techniques have not been implemented broadly.

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Chapter 9

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Summary

The past two decades have shown remarkable advances in the prevention and treatment of cardiovascular disease (CVD), due to improvements in risk factor stratification and a better understanding of the atherosclerotic process. Patients can thereby be treated earlier and more adequately. The central role of renal function in CVD is addressed in part I of this thesis. Imaging techniques to study the renal artery are assessed in part II, with both MRI (magnetic resonance imaging) and angiography. Part III describes the STAR trial, about the treatment of patients with renal impairment and atherosclerotic renal artery stenosis (ARAS). ***Chapter 1*** offers a short introduction about renovascular disease and related renal function. Renal dysfunction is increasingly being recognized as an important and independent risk factor for future CVD, in several subgroups op patients. Renal function seems to have a strong relationship with atherosclerosis, a generalized process which starts early in life. Renal function impairment in patients with ARAS is potentially reversible. Therefore, much effort is put in diagnostic and therapeutic research for ARAS, and in the search for predictors of outcome after treatment. Eventually, we want to be able to better select patients who will benefit from treatment. Patients with ARAS have a stenosis as well as generalized atherosclerosis. The stenosis can be treated with stent placement. Medication with blood pressure and lipid-lowering drugs might help restore the damage caused by atherosclerosis in the kidney.

Part I: Renal function, the Cinderella of cardiovascular risk profile

Much research has been performed to assess the effect of renal function on cardiovascular morbidity and mortality. This was studied in the general population, but also in subgroups of patients with hypertension and heart failure. The SMART study (Second Manifestations of ARTerial disease) includes patients with a risk factor for, or a manifestation of CVD, referred to the University Medical Center Utrecht. The participants undergo a vascular screening comprising laboratory tests, several imaging tests and they are asked to fill in a questionnaire. One of the aims of SMART is to study predictors of future CVD. For the purpose of the studies described in this part of the thesis, SMART patients with manifest vascular disease were selected. We demonstrated that there is indeed a strong relationship between atherosclerosis and renal function. We found that in patients with more severe atherosclerosis, the decrease in renal size and function with age was more pronounced than in patients with less severe atherosclerosis (***chapter 2***). Patients with manifest arterial disease have a higher risk of developing new symptoms of atherosclerosis. The traditional risk factors of CVD play a role, but also moderate to severely impaired renal function was demonstrated to be an independent predictor (***chapter 3***). In literature, renal function is referred to as the Cinderella of the cardiovascular risk profile, as it was present all along but suddenly has emerged as an important factor in CVD. Whether this is a causal relationship remains to be determined.

Part II: Imaging and intervention of the renal artery

ARAS is associated with hypertension and impaired renal function. Much uncertainty remains as far as the diagnosis and treatment of ARAS is concerned. The development of new and non-invasive imaging techniques might offer a tool to identify a subgroup of patients, which will benefit from certain treatments.

The etiology of renal dysfunction in ARAS is multifactorial and complex. The fact that the kidneys come in pairs, but having only one renal function adds to that complexity. MRI offers a means to assess anatomical as well as functional information about the kidney, in a non-invasive way. An aspect that is related to renal damage is the renal blood flow. Other parameters such as the resistance of the renal parenchyma can be distracted form the blood flow profile. In ***chapter 4*** we measured the blood flow in the renal arteries in healthy volunteers, and established whether these measurements were reproducible. To apply a new method, it is important that the measurements are feasible, reproducible and representative. In the relatively small and mobile renal arteries, the measurement of renal blood flow was difficult, with limited reproducibility, and this method is therefore not useful. Until the end of the 90s, stent placement was the treatment of choice for ARAS. Stent placement offered a better long term patency compared to balloon dilatation alone. However, a recurrent stenosis can occur in the stent. In-stent stenosis can be treated with balloon dilatation in the stent or placement of a second stent. In ***chapter 5*** we assessed the technical success rate of this re-intervention after one year. Our findings show that in-stent restenosis can well be treated by re-intervention, with a 75% success rate after one year.

Part III: Prevention of renal function loss in patients with atherosclerotic renal artery stenosis

Stent placement has been proved to be a feasible technique in the treatment of ARAS, with good long term patency of the renal arteries. However, evidence for the superiority of stent placement compared to medical treatment alone in terms of renal function, is lacking. Observational, uncontrolled studies on renal artery stenting are promising, but medical therapy has improved as well. Especially the introduction of statins seems to offer a beneficial effect.

In a randomized trial, the costs (real costs, but also costs in terms of complications from the intervention) are weighed against the benefits (stabilization or improvement in renal function). The STAR trial was designed to assess the benefit of STent placement and blood pressure and lipid-lowering for the prevention of progression of renal dysfunction caused by Atherosclerotic ostial stenosis of the Renal artery. In ***chapter 6*** we describe the rationale and design of the trial. Patients with impaired renal function (defined as a creatinine clearance <80 mL/min per 1.73 m^2 body surface) and a >50% renal artery stenosis caused

by atherosclerosis were included and randomized to medical treatment only or medical treatment plus stent placement of the renal artery. In both groups, medical treatment consisted of blood pressure and lipid-lowering drugs and a statin. The patients were furthermore advised to stop smoking. Patients were followed for 2 years and compared in terms of renal function. The primary end point was defined as >20% decrease in creatinine clearance compared to baseline. These results are described in ***chapter 7***. There is no statistically significant difference between the patients in the medication or the stent group. However, serious complications related to the stent placement procedure occurred in the stent group, with a mortality rate of 3%. There seems to be a beneficial effect of stent placement in patients with a unilateral stenosis instead of a bilateral stenosis. This finding will need to be confirmed after a longer follow-up. The findings from the STAR study show that the balance between preservation of renal function by improved medication and the adverse events following stent placement is not in favor of stent placement. These patients should primarily be treated conservatively.

In ***chapter 8*** the results of these studies are interpreted and their potential implications are discussed. On the one hand, the impact of impaired renal function in a patient with manifest arterial disease is highlighted. The exact mechanisms responsible for this relationship are still unclear. Impairment of the endothelial function probably plays a role. Patients with impaired renal function should be traced in an early stage and their risk profile modified. On the other hand, the preservation of renal function in renovascular disease is discussed. Impaired renal function in ARAS patients has multiple etiologies and therefore its treatment is not straightforward. The findings of the STAR trial favor a conservative therapeutic approach to patients with ARAS, focused on cardiovascular risk factor management. Future studies may identify a subgroup of patients who will benefit from stent placement.

Conclusions

1. Patients with more severe atherosclerosis have a faster decline in renal function and size with age, than patients with less severe atherosclerosis.
2. Screening of patients for new or recurrent vascular disease is very important. Moderately to severely impaired renal function is an independent predictor for adverse vascular outcomes.
3. Measurement of blood flow in the renal arteries with MRI is difficult and has limited reproducibility.
4. In-stent stenoses can be treated successfully with balloon dilatation or placement of a second stent, with good technical success rates after a year.
5. Treatment of renal function impairment in ARAS patients requires good risk factor modification. Stent placement in addition to medication does not further prevent progression of renal failure.

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Samenvatting

In de laatste 20 jaar is er aanzienlijke vooruitgang geboekt in de preventie en behandeling van cardiovasculaire ziekte (hart- en vaatziekte) op basis van atherosclerose (slagader-verkalking). Deze vooruitgang kan in belangrijke mate worden toegeschreven aan de verbeterde screening op risicofactoren en een toegenomen kennis van de pathologie van atherosclerose. Daarmee kunnen patiënten in een vroeger stadium en op een adequate manier worden behandeld. De centrale rol van de nierfunctie in deze cardiovasculaire problematiek wordt in deel I onderzocht. Vervolgens worden in deel II beeldvormende technieken bestudeerd van de nierarterie, enerzijds met MRI (magnetische resonantie imaging) en anderzijds met angiografie. In deel III wordt de STAR studie beschreven. Hierin wordt de behandeling van patiënten met een nierfunctiestoornis en een nierarteriestenose (nierslagadervernauwing, NAS) op basis van atherosclerose onderzocht.

In ***hoofdstuk I*** wordt een korte introductie gegeven over renovasculaire ziekte (vaatziekte van de nier) en de daaraan gerelateerde nierfunctie. Nierfunctiestoornis wordt steeds vaker en in verschillende subgroepen erkend als een belangrijke, onafhankelijke risicofactor voor cardiovasculaire ziekte. De nierfunctie lijkt nauw samen te hangen met atherosclerose, een gegeneraliseerd proces dat al op vroege leeftijd begint. De nierfunctieproblematiek bij patiënten met een atherosclerotische NAS is potentieel reversibel en er wordt daarom veel onderzoek gedaan naar de diagnostiek en behandeling van NAS, en naar voorspellers van een betere uitkomst na behandeling. Wij zouden graag de patiënten die baat hebben bij een behandeling beter willen kunnen selecteren. Patiënten met een atherosclerotische NAS hebben zowel een stenose als gegeneraliseerde atherosclerose. Middels stentplaatsing (een metalen buisje dat in het bloedvat geplaatst wordt) zou de stenose verholpen kunnen worden. Medicijnen in de vorm van o.a. bloeddruk- en cholesterol-verlagende middelen zouden de schade door atherosclerose kunnen helpen verminderen.

Deel I: Nierfunctie, de "Assepoester" van het cardiovasculaire risico profiel

Er is reeds veel onderzoek gedaan naar de invloed van nierfunctie op cardiovasculaire ziekte en sterfte, zowel in de algemene bevolking als in subgroepen van patiënten met hypertensie of hartfalen. In het SMART onderzoek (Second Manifestations of ARTerial disease) worden patiënten ingesloten met een risicofactor voor, of een uiting van cardiovasculaire ziekte die verwezen zijn naar het Universitair Medisch Centrum Utrecht. De deelnemers ondergaan een vasculaire screening die bestaat uit laboratoriumonderzoeken, verschillende beeldvormende onderzoeken en het invullen van een vragenlijst. Een van de doelstellingen van SMART is het onderzoeken van voorspellers voor (nieuwe) cardiovasculaire ziekte. Voor de studies beschreven in dit deel van het proefschrift werden patiënten geselecteerd

met een uiting van vaatziekte. Wij tonen aan dat er een nauwe relatie bestaat tussen atherosclerose en nierfunctie. Allereerst zien wij dat een ernstigere mate van atherosclerose de natuurlijke afname van nierfunctie en nierlengte met de leeftijd versnelt (***hoofdstuk 2***). Voorts hebben patiënten die al een uiting hebben van vaatziekte een aanzienlijke kans op nieuwe of recidiverende symptomen van atherosclerose. De klassieke risicofactoren spelen daarbij een rol, maar ook een matig tot ernstig gestoorde nierfunctie blijkt een onafhankelijke voorspeller te zijn (***hoofdstuk 3***). In de literatuur wordt de nierfunctie ook de "Assepoester" van het cardiovasculaire risicoprofiel genoemd. Het is ongemerkt altijd al in ons midden is geweest en nu plotseling ontpopt het zich als een belangrijke factor. Het is nog onduidelijk of het een causale relatie betreft.

Deel II: Beeldvorming en interventie in de nierslagader

Atherosclerotische NAS gaat veelal gepaard met hypertensie (een verhoogde bloeddruk) en een gestoorde nierfunctie. Over de behandeling en diagnose van NAS is veel onderzoek gedaan en wordt nog veel gediscussieerd. De ontwikkeling van nieuwe, voor de patiënt niet belastende (non-invasieve) technieken biedt mogelijk een middel om een subgroep van patiënten te identificeren die baat zullen hebben bij een specifieke behandeling.

Nierfunctiestoornis bij NAS is multifactorieel en complex. Het hebben van twee nieren en één nierfunctie draagt bij aan die complexiteit. Middels MRI is het mogelijk zowel anatomische als functionele informatie te krijgen op een non-invasieve manier. Een aspect dat samenhangt met de nierschade is de bloedstroom. Uit het bloedstroomprofiel zouden vervolgens andere parameters als de weerstand van het nierweefsel gemeten kunnen worden. In ***hoofdstuk 4*** hebben wij met MRI de bloedstroom in de nierslagers gemeten bij gezonde vrijwilligers en onderzocht of deze metingen reproduceerbaar zijn. Om een nieuwe methode toe te passen is het belangrijk dat de meting uitvoerbaar, reproduceerbaar en representatief is. In de relatief kleine en beweeglijke nierslagaders blijkt de bloedstroom lastig te meten, met een beperkte reproduceerbaarheid en lijkt de methode dus niet goed bruikbaar.

Tot aan het einde van de jaren 90 was de stentplaatsing de standaard behandeling voor NAS op basis van atherosclerose. Hierbij bood de stent een betere doorgankelijkheid van het vat op lange termijn vergeleken met alleen ballon dilatatie. Echter, in een klein percentage van de patiënten kunnen ook in de stent recidief stenosen optreden. Deze kunnen worden behandeld met een ballon dilatatie in de stent of plaatsing van een tweede stent. In ***hoofdstuk 5*** hebben wij onderzocht wat het effect van deze re-interventie was na een jaar. Uit onze resultaten blijkt dat op deze manier re-stenosen goed te behandelen zijn en dat na een jaar nog 75% van de vaten doorgankelijk is.

Deel III: Voorkómen van nierfunctieachteruitgang bij patiënten met atherosclerotische nierarteriestenose

De stentplaatsing heeft bewezen een goede techniek te zijn en ook op lange termijn goede doorgankelijkheid van de niervaten te bieden. Er blijkt echter nog geen wetenschappelijk bewijs te bestaan waaruit blijkt dat stentplaatsing beter is dan medicamenteuze (conservatieve) therapie, voor wat betreft de nierfunctie. Observationele studies (zonder controle groep) naar stentplaatsing zijn veelbelovend. Ondertussen staan de ontwikkelingen vanuit de farmaceutische wereld echter niet stil. Met name de behandeling met statines (cholesterolverlagende middellen) kan nog veel winst opleveren.

Dit probleem vraagt om een gerandomiseerd onderzoek, om zo de kosten (feitelijke kosten, maar ook complicaties van de interventie) af te wegen tegen de baten (stabilisatie of verbetering in nierfunctie). De STAR studie onderzoekt de doelmatigheid van stentplaatsing en lipiden- en bloeddrukverlagende therapie ter voorkoming van progressie van nierinsufficiëntie door atherosclerotische NAS in de nierslagader. In ***hoofdstuk 6*** beschrijven wij het ontwerp van de STAR studie. Patiënten met een gestoorde nierfunctie (creatinine klaring <80 mL/min per 1.73 m^2 lichaamsoppervlakte) en een >50% NAS op basis van atherosclerose worden ingesloten en gerandomiseerd naar behandeling met alleen medicijnen of medicijnen plus stentplaatsing in de nierarterie. De medicamenteuze therapie bestaat in beide groepen uit bloeddruk- en lipidenverlagende middelen en aspirine. Voorts worden alle patiënten geadviseerd te stoppen met roken. De patiënten worden in beide groepen vervolgd en in eerste instantie na 2 jaar vergeleken voor wat betreft hun nierfunctie. Het primaire eindpunt is gedefinieerd als een 20% achteruitgang van de creatinine klaring vergeleken met het begin van de studie. In ***hoofdstuk 7*** worden deze resultaten beschreven. Er blijkt geen significant verschil tussen de patiënten in de stentgroep en de medicatiegroep. In de stentgroep kwamen echter ernstige complicaties voor ten gevolge van de stentplaatsing, met zelfs 3% sterfte. Er lijkt een mogelijk betere uitkomst na stentplaatsing bij patiënten met een enkelzijdige in plaats van dubbelzijdige stenose. Deze bevinding zal na een langere follow-up bevestigd moeten worden. Uit het STAR onderzoek wordt geconcludeerd dat de verbeterde medicijnen en de complicaties van de stent ervoor zorgen dat de stent geen voordeel biedt boven het geven van alleen medicijnen en dat dus een conservatieve behandeling de voorkeur heeft.

In ***hoofdstuk 8*** wordt ingegaan op de interpretatie en de mogelijke toepassingen van de resultaten van de in dit proefschrift beschreven onderzoeken. Enerzijds wordt het belang van een gestoorde nierfunctie bij patiënten met een uiting van vaatziekte belicht.

Welke mechanismen aan deze nauwe relatie ten grondslag liggen is nog onduidelijk. Een gestoorde endotheelfunctie zou een rol kunnen spelen. Patiënten met een gestoorde nierfunctie zouden actief en in een vroeg stadium opgespoord moeten worden zodat hun risicoprofiel aangepast kan worden. Anderzijds wordt het behandelen van de nierfunctie in het kader van de renovasculaire ziekte besproken. De oorzaak van nierfunctiestoornis bij atherosclerotische NAS patiënten is meerledig en daarmee de behandeling niet eenvoudig. Aan de hand van de resultaten uit de STAR studie heeft de conservatieve therapie de voorkeur. Mogelijk zullen er in de toekomst subgroepen van patiënten zijn die wel baat zullen hebben bij stentplaatsing.

Conclusies

1. Patiënten met ernstige atherosclerose hebben een snellere afname van de nierfunctie en nierlengte met de leeftijd dan patiënten met minder ernstige atherosclerose.
2. Het screenen van patiënten voor nieuwe en recidiverende vaatziekte is van groot belang. Een matig tot ernstig gestoorde nierfunctie is voorspellend voor een slechte prognose.
3. Het meten van de bloedstroom in de nierslagaders met MRI is lastig uitvoerbaar en heeft een beperkte reproduceerbaarheid.
4. In-stent stenosen kunnen met behulp van ballon dilatatie of plaatsing van een tweede stent worden behandeld, met een goede doorgankelijkheid van de stent na een jaar.
5. De behandeling van nierfunctiestoornis bij atherosclerotische NAS patiënten behelst een goede aanpak van de cardiovasculaire risico factoren. Stentplaatsing naast medicatie voorkomt geen achteruitgang in nierfunctie.

Chapter 9

Dankwoord

De totstandkoming van dit proefschrift leek vaak overeenkomsten te vertonen met de bouw van de Sagrada Familia van Gaudi, er werd hard aan gewerkt maar het einde was nog lang niet in zicht. Maar nu is het zover, mijn bouwwerk is af! Het was een zeer leerzame tijd waarin ik met veel mensen heb samengewerkt, die ieder hun steentje hebben bijgedragen. Een aantal wil ik daarom graag met name bedanken.

Prof. dr. W.P.Th.M. Mali, beste Willem, je enthousiasme voor de wetenschap werkt aanstekelijk en inspirerend. Ik heb erg veel waardering voor je inspanningen een goede onderzoekssfeer te creëren binnen de afdeling radiologie en in samenwerking met andere divisies. Ik heb het als een voorrecht ervaren daar deel van uit te mogen maken. Je deur stond altijd open en je begeleiding was zeer stimulerend. Hartelijk dank ook voor je persoonlijke belangstelling en inzet voor mijn toekomst.

Prof. dr. Y. van der Graaf, beste Yolanda, ik heb veel bewondering voor je manier van werken en begeleiden. Je nuchtere en pragmatische aanpak ligt mij wel. Met veel plezier denk ik terug aan de gezellige besprekingen op je kamer, die ik vol goede moed en inspiratie verliet. Mijn 'lijken' zijn toch nog goed terecht gekomen. Ik vond het erg leuk ten tijde van jouw oratie in je huid te mogen kruipen en even te proeven aan het leven van een vrouwelijke hoogleraar in deze mannenwereld. Ik ben blij dat je mijn promotor wilde zijn.

Dr. J.J. Beutler, beste Jaap, hartelijk dank voor de goede samenwerking en je noodzakelijke klinische kijk op de gang van zaken en interpretatie van de resultaten. De langdurige samenwerking tussen onze afdelingen, en jouw persoonlijke rol daarin, heeft mooie vruchten afgeworpen. Je vertrek naar Den Bosch was dan ook duidelijk te merken. De STAR studie was ook jouw 'kindje', hartelijk dank dat ik er voor heb mogen zorgen.

Graag wil ik de leescommissie, Prof. dr. F.L. Moll, Prof. dr. G. Pasterkamp, Prof. dr. A. Algra, Prof. dr. P.W. de Leeuw en Prof. dr. J.A. Reekers bedanken voor het beoordelen van mijn manuscript.

Graag wil ik de STAR onderzoekers uit de verschillende ziekenhuizen bedanken voor het includeren en vervolgen van de patiënten: zonder jullie was STAR niet mogelijk geweest. Het was niet alleen voor mij, maar ook voor jullie een onderneming met een lange adem. Hartelijk dank voor jullie inzet en enthousiasme. Op naar de vijfjaars follow-up!

Binnen SMART was ik een beetje een buitenbeentje, maar heb er met veel plezier samen gewerkt. Allereerst wil ik de SMART studiegroep en de SMART medewerkers bedanken, wat is het toch een mooi sneeuwbal-project. Ale Algra, jou wil ik bedanken voor je verfijnde kritiek op mijn artikelen. Je input bij het brainstormen rond mijn studies heb ik zeer gewaardeerd. Michael Edlinger, hartelijk dank voor je hulp bij mijn soms lastige analyses. SMART-dames (inmiddels SMARTies), met name Loes en Vera, bedankt voor de goede samenwerking en jullie gezelligheid.

Ook wil ik Chris Bakker en Niels Blanken (afdeling radiologie) en Jan Verwoerd (Philips) bedanken voor hun toewijding aan de klinische wetenschap en hun hulp bij het verfijnen van het nierprotocol voor mijn flow studie. Mede dankzij jullie lukte het mij de MRI technieken (zo ongeveer) te begrijpen.

Het trialbureau radiologie ben ik zeer veel dank verschuldigd voor de logistieke ondersteuning. Lieve Anneke**,** mijn rots in de branding. Je efficiëntie en doortastendheid zijn onbetaalbaar. Dankzij jou kon ik zonder zorgen aan mijn opleiding beginnen terwijl jij de STAR studie draaiende hield. We hebben vele uren samen in je Toyota doorgebracht om de STAR-centra te bezoeken, het was vooral ook een gezellige samenwerking. Beste Cees**,** als ervaren datamanager leek je nooit te schrikken als ik weer eens met een verzoekje kwam. Hartelijk dank voor het bouwen van een analyseerbare database. Vooral wil ik je ook hartelijk bedanken voor de lay-out van het proefschrift. Met je "gefröbel" wist je mijn smaak goed tot uiting te laten komen.

Mijn wetenschappelijke activiteit zijn erg verspreid geweest over de afgelopen jaren, in vele kamers en met vele kamergenoten. Ik vond het erg verfrissend en stimulerend met zo'n diverse groep onderzoekers samen te werken. Uiteenlopende projecten: van benen, breinen, harten, borsten of longen; bij mannen, vrouwen of konijnen; dwarsdoorsnede onderzoek, gerandomiseerde studie, meta-analyse of review: alle smaken waren vertegenwoordigd. Epiraders, Julianen en onderzoekers van ImagO, bedankt voor de gezelligheid en het delen van wetenschappelijk lief en leed. Een aantal collega's wil ik in het bijzonder bedanken. Willemijn, Daisy, Maarten, Maurice en Paul, we vormden samen een gezellig "kippenhok". Joke, je timing was perfect. Aan jou had ik weer een maatje. Lisa, dank voor je uitstekende parate kennis van de epidemiologie en trucjes in SPSS.

Via deze weg wil ik ook de stafleden van de radiologie bedanken. Mede dankzij Prof. dr. J.P.J. van Schaik is het mogelijk geweest mijn opleiding te combineren met het wetenschappelijk onderzoek. Inmiddels heb ik verschillende generatie AIOS op de werkvloer mee gemaakt, velen hebben mij al ruimschoots ingehaald. Hartelijk dank voor jullie collegialiteit en belangstelling in de vordering van mijn werk. Negatieve uitkomsten publiceren minder makkelijk hebben jullie al wel gemerkt! Annemieke, Mark en Jet wil ik in het bijzonder bedanken voor de goede samenwerking als hoofdassistenten. Kleine stappen voor een assistent, grote passen voor de opleiding, of andersom.

Dames van het stafsecretariaat, jullie hebben mijn werk het afgelopen jaar een stuk aangenamer weten te maken. Marja, Linda en Meike, bedankt voor jullie steun en welkome afleiding.
Hartelijk dank voor de multimedia ondersteuning van de fotografie afdeling met Jan, Roy, Karin en Eugène. Nooit was iets teveel gevraagd.

Lieve Joke, hartelijk dank dat je nu ook aan mijn zijde wilt staan. Ik waardeer je enorm als wetenschapper en als vriendin. Ik heb bewondering voor hoe jij in het leven staat. Je enthousiasme is aanstekelijk. Zoals ik al zei vond ik in jou een maatje en dat is heel vaak heel fijn.

Lieve Marieke, we hebben al vele mijlpalen samen gedeeld en in dat bewogen bestaan van ons heb ik altijd op jou terug kunnen vallen. Onze goede band vergaat niet. Ik waardeer je interesse in mijn projecten, zo attent als jij ken ik er geen één. Fijn dat je ook hier mijn 'Maître de Cérémonie' wilt zijn.

Ik bof met een goed stel vrienden en vriendinnen, die indirect ook een bijdrage hebben geleverd aan dit proefschrift. Georges Brassens zong "L'amitié n'exige rien en échange, que de l'entretien". Er komen nu betere tijden aan. Met name Dana en Annemarie, hartelijk dank voor jullie 'verlichtende' vriendschap en gezelligheid. We hadden het geografisch niet beroerder kunnen treffen. Fijn dat het toch steeds weer lukt om samen af te spreken.

Lieve Katrien, de creatieve genen zitten duidelijk meer bij de van de Camps! Hartelijk dank voor je mooie ontwerp en je inzet in voor jou ook zeer drukke tijden.

Lieve Hetty en Thieu, jullie maakten mijn debuut als wetenschapper mee in Los Angeles, met de schapen van Koos. Jullie interesse voor mijn onderzoek en zijn vorderingen de afgelopen jaren zijn hartverwarmend geweest. Bedankt ook voor jullie herhaaldelijke initiatieven om de kinderen mee naar Giethmen te nemen.

Lieve Papa en Mama, ik dank jullie voor een fantastische en liefdevol 'thuis'. Jullie hebben het mij altijd mogelijk gemaakt om mezelf te ontplooien en hebben mij daar ook vaak actief in gestimuleerd en gesteund. Jullie niet-aflatende belangstelling voor mijn onderzoek en inspanningen goed op de hoogte te zijn van wat ik deed, heb ik bijzonder gewaardeerd. Dit proefschrift is ook jullie verdienste.

Lieve Joris, bedankt voor je vertrouwen dat het als vanzelfsprekend allemaal goed zou komen. Jouw liefde en steun hebben me veel geholpen om deze klus te klaren en ook nog van het leven te genieten. Ik ben heel blij met jou en onze "cailloux du tonnerre", Oscar en Emilie.

Liesbeth

Chapter 9

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Liesbeth Bax was born on August 27th, 1974, in Bron, France. She grew up abroad, living in France, the Netherlands, Switzerland and Spain. She obtained her French scientific Baccalauréat in 1992 at the Lycée Français de Madrid (Spain). She then started her medical training at the University Medical Center in Utrecht. After working on a research project at the University of California, Los Angeles (USA, Prof. B.J. Koos), she obtained her medical degree in September 1999. In December that year she started to work on the projects described in this thesis as a research physician for the STAR trial at the department of radiology, University Medical Center Utrecht, under supervision of Prof. dr. W.P.Th.M. Mali, Prof. dr. Y. van der Graaf and dr. J.J. Beutler. After three years of research, she began with her radiology residency in January 2003 at the University Medical Centre Utrecht (Prof. dr. J.P.J. van Schaik). One year of her residency was performed in Paris (France) at the Hôpital Européen Georges Pompidou (Prof. G. Frija). She interrupted her radiology training to finish her research on the STAR trial, which lead to the completion of this thesis. She is currently a fourth-year resident.
She is married to Joris Peters and they have two children, Oscar (2005) and Emilie (2007).

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SMART STUDY

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